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July 1977

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16. ABSTRACT

This report reviews the potential environmental hazard from use of the halogenated benzenes. Major focus is in the commercially important chlorinated benzenes, though fluorinated, brominated and iodinated benzenes are also discussed as well as mixed halogen compounds. Hexachlorobenzene is not included in this study except where information relates to trends within the group of chlorinated benzenes.

Chlorinated benzenes are used as solvents, chemical intermediates, for moth repellency and as space odorizers. Several chlorinated benzenes have been detected in drinking and raw water sources throughout the U.S. p-Dichlorobenzene has been found in human blood samples from New Orleans, and with 1,2,4,5-tetrachlorobenzene and hexachlorobenzene in human adipose tissue samples collected in Tokyo, Japan.

While of comparatively low acute toxicity, chronic or 'subacute' efffects are seen at fairly low concentrations. These effects include: porphyria, necrosis of liver, kidneys and lungs, and possible blood abnormalities. Several of the chlorinated benzenes are known mutagens in plants. Carcinogenic studies completed were of a short duration and must be considered inconclusive until studies are repeated using current methodologies.

The extent of metabolism of these compounds depends on the degree of substitution, the position(s) of substitution and the type of halogen.

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HALOGENATED BENZENES

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EXECUTIVE SUMMARY

Halogenated benzenes are substituted benzene compounds containing fluorine, chlorine, bromine and/or iodine. Substitution may involve replacement of one to six hydrogen atoms of the benzene by a halogen. This report examines all fluoro-, chloro-, bromo- and iodobenzenes from the mono- to the hexasubstituted. Hexachlorobenzene, which has been the subject of several related studies, is discussed only when data for this compound illustrate a trend within the group of chemicals, or help clarify the significance of given information.

Halogenated benzenes are a group of chemically stable compounds. The chlorinated benzenes are of particular industrial importance. Production of monochlorobenzene exceeds 300 million pounds per year, while production of _o_- and _p_-dichlorobenzene, 1,2,4-trichlorobenzene and 1,2,4,5-tetrachlorobenzene is in excess of tens of millions of pounds each per annum.

Chlorinated benzenes are used as solvents, as heat transfer and dielectric fluids, as chemical intermediates, and as deodorizers and insect repellents. These latter two uses have both industrial and household applications. As intermediates, chlorinated benzenes are precursors of phenolic compounds, diazonium salts and various herbicides.

Environmental contamination occurs as a result of manufacture, use, disposal and possibly transportation of chlorinated benzenes. _p_-Dichlorobenzene has been detected in human blood samples taken in the New Orleans area. A recent Japanese study has shown the presence of _p_-dichlorobenzene, 1,2,4,5-tetrachloro- and hexachlorobenzene in human fatty tissue, with the para-compound also detected in human blood. Chlorinated benzenes have been detected in fish, in raw water sources and even in drinking water. They have also been found in the air and soil. Brominated benzenes have been located in raw water sources and in drinking water.

Lower halogenated compounds are absorbed by mammals through the intact skin, the lungs and the gastrointestinal system. Higher halogenated compounds tend to be poorly absorbed, though once in the system, they will accumulate in fatty tissue. All halogenated benzenes appear to be lipid soluble. Higher chlorinated benzenes resist biodegradation, though some decomposition occurs for lower chlorinated compounds.

Acute effects of exposure to halogenated benzenes include either stimulation or depression of the central nervous system (CNS). Acute depression may result in respiratory failure and death. There are animal species differences in the ability of halogenated benzenes to produce CNS effects. The extent of metabolism of these compounds tends to decrease with greater number of halogen substitutions. Again there are species differences in ability to metabolize halogenobenzenes.

Chronic effects due to exposure include porphyria, necrosis of liver, lung and kidney and possible blood abnormalities. Pentachlorobenzene was shown to be carcinogenic in mice in one test system, but there is little evidence that the other compounds are carcinogenic. However, chronic studies completed in the past were either of a short duration or inconclusive. Hence, carcinogenic testing of those chlorinated benzenes found in the environment should be performed according to current methodologies.

Several chlorinated benzenes are known to interfere with cell division in higher plants and in some microorganisms. There are no reports of mutagenesis in mammals. There are indications that both pentachlorobenzene and hexachlorobenzene are teratogenic. No teratogenicity studies have been performed for the lower halogenated compounds.

Considering the extent to which chlorinated benzenes are entering the environment, and the evidence suggesting bioaccumulation, there is a need to know more about possible chronic effects of exposure to these compounds. There is an accompanying need to establish the behavior of the halogenated benzenes once in the environment.

I. PHYSICAL AND CHEMICAL DATA

1. Chemical Structure

The halogenated benzenes to be discussed in this report include all fluoro-, chloro-, bromo- and iodobenzenes from the mono- to the hexa-substituted. Hexachlorobenzene is not included except when data for this compound illustrate a trend within the group of chemicals, or help clarify the significance of given information. Mixed halogenated benzenes are discussed wherever information was found. No halogenated compounds with other substituents in the ring are part of this study.

Figure 1 lists all possible configurations for the halogenated benzenes.

2. Nomenclature

There are a number of ways to name each of the compounds discussed in this study. Synonyms and trade names for the commercially important chlorinated benzenes are found in Table 1. Chemical names for the other halogenated compounds follow the same pattern, e.g. monobromobenzene: phenyl bromide, benzene bromide, etc.

Abbreviations used for chlorinated compounds are those listed in the same table. Please note that where found PCB stands for polychlorinated biphenyl as is the usual practice, and not for p-dichlorobenzene which has sometimes been used.

FIGURE 1

CONFIGURATIONS OF THE HALOGENATED BENZENES

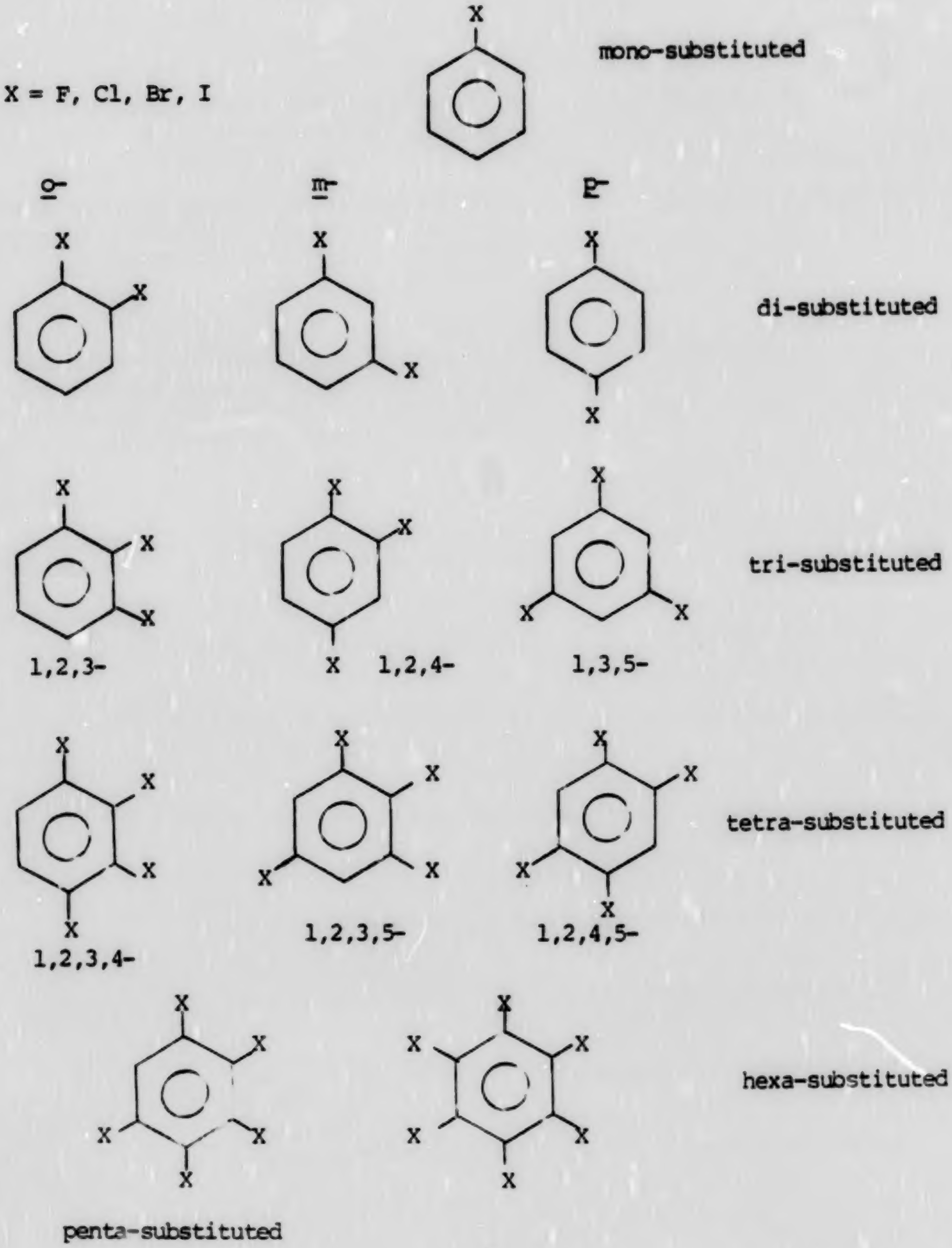
X = F, Cl, Br, I
X
mono-substituted
o-
m-
p-
X
X
X
X
X
X
di-substituted
X
X
X
X
X
X
X
X
X
tri-substituted
1,2,3-
1,2,4-
1,3,5-
X
X
X
X
X
X
X
X
X
X
X
X
tetra-substituted
1,2,3,4-
1,2,3,5-
1,2,4,5-
X
X
X
X
X
X
X
X
X
X
X
hexa-substituted
penta-substituted

TABLE 1

SYNONYMS AND TRADE NAMES FOR CHLORINATED BENZENES

Monochlorobenzene:	chlorobenzene; chlorobenzol; benzene chloride; phenyl chloride; MCB
o-Dichlorobenzene:	orthodichlorobenzene; *ortho*-dichlorobenzene; *ortho*-dichlorobenzol; 1,2-dichlorobenzene; ODB; ODCB; Dizene®; Chloroben®; Dowtherm® E
p-Dichlorobenzene:	paradichlorobenzene; *para*-dichlorobenzene; *para*-dichlorobenzol; 1,4-dichlorobenzene; PDB; PDCB; Di-chloricide®; Paracide®; Paradi®; Paradow®; Paramoth®; Santochlor®
m-Dichlorobenzene:	metadichlorobenzene; *meta*-dichlorobenzol; *meta*-dichlorobenzene; 1,3-dichlorobenzene
1,2,3-Trichlorobenzene:	1,2,3-trichlorobenzol; 1,2,3-TCB
1,2,4-Trichlorobenzene:	1,2,4-trichlorobenzol; 1,2,4-TCB; uns-trichlorobenzene
1,3,5-Trichlorobenzene:	1,3,5-trichlorobenzol; 1,3,5-TCB; sym-trichlorobenzene
1,2,3,4-Tetrachlorobenzene:	1,2,3,4-tetrachlorobenzol
1,2,3,5-Tetrachlorobenzene:	1,2,3,5-tetrachlorobenzol
1,2,4,5-Tetrachlorobenzene:	1,2,4,5-tetrachlorobenzol
Pentachlorobenzene:	quintochlorobenzene; QCB

3. Physical Properties of the Pure Material

The monohalogenated benzenes are all colorless, neutral, relatively volatile liquids with a pungent aromatic odor. The boiling points are sufficiently different (see Table 2) that they may be separated by fractional distillation. They are all denser than water, as are all of the halogenated benzenes and most of the mixed halogenated benzenes (see Table 3).

Monohalobenzenes are almost insoluble in water (see Table 4). If monohalobenzenes accumulate in raw water systems, they tend to sink. Because of their comparatively high volatility, there may be a greater tendency to accumulate in still lake waters rather than fast moving streams and rivers (see Section III).

TABLE 4
SOLUBILITIES OF MONOHALOGENATED BENZENES
(Seidell, 1952)

Compound	Solubility
Monochlorobenzene	0.0488 g/100g @ 30°C
Monofluorobenzene	0.154 g/100g @ 30°C
Monobromobenzene	0.0446 g/100g @ 30°C
Monoiodobenzene	0.034 g/100g @ 30°C

Monohalogenated benzenes have a high solubility in nonpolar solvents (see Table 5). They are all highly soluble in lipids. Partition coefficient data for several chlorinated benzenes is found in Table 49. For the limited data presented, there was an increase in partition coefficient from mono- to hexachlorobenzene. Lu and Metcalf (1975) reported a positive correlation between partition coefficient and degree of bioaccumulation.

Monochlorobenzene forms azeotropic mixtures with a number of solvents (see Table 7).

The monoderivatives are classified as flammable liquids. Flash point data and explosive limits are presented in Table 8. Because of the possibility of combustion with oxidizing agents, special care must be taken in handling during manufacture, use and transportation (see Section IID).

TABLE 2

PHYSICAL PROPERTIES OF HALOGENATED BENZENES
(Feast and Musgrave, 1971; Weast, 1976)

Compound	Melting Point (°C)	Boiling Point (°C)	Density (gm/cm^3)	Refractive Index
Monofluorobenzene	-41.9	85	d_4^{15} 1.0309	n_D^{20} 1.4667
o-Difluorobenzene	-34	91	d_4^{25} 1.1496	n_D^{20} 1.4452
m-Difluorobenzene	-59.3	83	d_4^{20} 1.1572	n_D^{20} 1.4410
p-Difluorobenzene	-13.0	89	d_4^{20} 1.1716	n_D^{20} 1.4421
1,2,3-Trifluorobenzene	-13.5	95		n_D^{20} 1.4230
1,2,4-Trifluorobenzene	-35	88		
1,3,5-Trifluorobenzene	- 5.5	75.5	d_4^{20} 1.277	n_D^{20} 1.4140
1,2,3,4-Tetrafluorobenzene	-42	95	d_4^{25} 1.422	n_D^{20} 1.4069
1,2,3,5-Tetrafluorobenzene	-48	83	d_4^{25} 1.410	n_D^{25} 1.4011
1,2,4,5-Tetrafluorobenzene	4	90	d_4^{25} 1.424	n_D^{20} 1.4045
Pentafluorobenzene	-48	85	d_4^{20} 1.531	n_D^{25} 1.3881
Hexafluorobenzene	5	80	d_4^{20} 1.6182	n_D^{25} 1.3761
Monochlorobenzene	-45.2	132.0	d_4^{15} 1.117	n_D^{51} 1.5275
o-Dichlorobenzene	-17.2	179.2	d_4^{25} 1.2973	$n_D^{20.4}$ 1.5485
m-Dichlorobenzene	-26.3	172	d_4^{25} 1.2799	$n_D^{20.9}$ 1.5457
p-Dichlorobenzene	53.0	174.5	d_4^{55} 1.2495	$n_D^{19.9}$ 1.5267
1,2,3-Trichlorobenzene	52.4	218		
1,2,4-Trichlorobenzene	16.6	213	d_4^{25} 1.4634	n_D^{25} 1.5524
1,3,5-Trichlorobenzene	63	208		
1,2,3,4-Tetrachlorobenzene	47.5	254		

TABLE 2 (continued)

Compound	Melting Point (°C)	Boiling Point (°C)	Density (gm/cm^3)	Refractive Index
1,2,3,5-Tetrachlorobenzene	51	246		
1,2,4,5-Tetrachlorobenzene	138	244	d_4^{22} 1.858	
Pentachlorobenzene	87	276	$d_4^{16.5}$ 1.8342	
Hexachlorobenzene	229	326	$d_4^{23.6}$ 1.5691	
Monobromobenzene	-30.6	156.2	d_4^{20} 1.4946	n_D^{20} 1.5597
o-Dibromobenzene	+ 6.7	225	d_4^{20} 1.956	n_D^{20} 1.6155
m-Dibromobenzene	- 7	220	d_4^{20} 1.952	n_D^{17} 1.6083
p-Dibromobenzene	+87.3	220	d_4^{100} 1.8322	n_D 1.5742
1,2,3-Tribromobenzene	88		2.658	
1,2,4-Tribromobenzene	44	275		
1,3,5-Tribromobenzene	119	271		
1,2,3,4-Tetrabromobenzene	47.5	254		
1,2,3,5-Tetrabromobenzene	98	329		
1,2,4,5-Tetrabromobenzene	173		d_4^{20} 3.072	
Pentabromobenzene	159	sub.	d_4^{20} 3.072	
Hexabromobenzene	326			
Monoiodobenzene	-31	188.5	d_4^{25} 1.823	$n_D^{17.8}$ 1.6213
o-Diiodobenzene	26.7	286	d_4^{20} 2.54	n_D^{20} 1.7179
m-Diiodobenzene	35	285	d_4^{20} 2.47	
p-Diiodobenzene	129	285		
1,2,3-Triiodobenzene	116	sub.		
1,2,4-Triiodobenzene	91.5	sub.		
1,3,5-Triiodobenzene	184	sub.		
1,2,3,4-Tetraiodobenzene	136	sub.		
1,2,3,5-Tetraiodobenzene	148	sub.		
1,2,4,5-Tetraiodobenzene	254	sub.		
Pentaiodobenzene	172	sub.		
Hexaiodobenzene	340-350			

TABLE 3

PROPERTIES OF MIXED HALOGENATED BENZENE DERIVATIVES
(Feast and Musgrave, 1971; Weast, 1976)

Name	Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Density (gm/cm^3)	Refractive Index
1-Bromo-2-chlorobenzene	191.46	-12	204	1.6382	1.5809
1-Bromo-3-chlorobenzene	191.46	-21	196	1.6302	1.5771
1-Bromo-4-chlorobenzene	191.46	67	196	1.576	1.5531
1-Bromo-2,3-dichlorobenzene	225.91	60	243	-	-
1-Bromo-3,5-dichlorobenzene	225.91	74	232	-	-
2-Bromo-1,3-dichlorobenzene	225.91	65	242	-	-
2-Bromo-1,4-dichlorobenzene	225.91	35	235	-	-
4-Bromo-1,2-dichlorobenzene	225.91	25	237	-	-
1-Bromo-3-fluorobenzene	175.01		151		
1-Bromo-2-fluorobenzene	175.01		57/22mm	-	-
1-Bromo-4-fluorobenzene	175.01	-17	152	1.4946	1.5604
1-Bromo-2-iodobenzene	282.92	2-5	257	2.2571	1.6618
1-Bromo-3-iodobenzene	282.92	- 9	252	-	-
1-Bromo-4-iodobenzene	282/92	92	251-252	-	-
1-Chloro-2-fluorobenzene	130.56	-43	138-140	1.2233	1.4968
1-Chloro-4-fluorobenzene	130.56	-28	130	1.226	1.4990
1-Chloro-2-iodobenzene	238.47	-	234-235	1.9515	1.6331
1-Chloro-3-iodobenzene	238.47	-	230	-	-
1-Chloro-4-iodobenzene	238.45	56-57	226-7	1.886	-
1-Fluoro-4-iodobenzene	222.00	-20	182	1.9523	1.5270
1-Fluoro-2-iodobenzene	222.00	-41.5	188	-	-
1,4-Dichloro-2-iodobenzene	272.90	21	250-1	-	-

TABLE 5

SOLUBILITIES OF HALOGENATED BENZENES
(Weast, 1976)

Compound	Water	Alcohol	Ether	Benzene	Chloroform
Monofluorobenzene	i	∞	∞	∞	—
Monochlorobenzene	i	∞	∞	vs	vs
1,2-Dichlorobenzene	i	s	s	∞	—
1,3-Dichlorobenzene	i	s	s	s	—
1,4-Dichlorobenzene	i	∞	∞	s	s
1,2,3-Trichlorobenzene	i	ss	vs	vs	—
1,2,4-Trichlorobenzene	i	ss	vs	—	—
1,3,5-Trichlorobenzene	i	ss	vs	vs	—
1,2,3,4-Tetrachlorobenzene	i	ss	vs	—	—
1,2,3,5-Tetrachlorobenzene	s (hot)	ss	s	s	—
1,2,4,5-Tetrachlorobenzene	i	ss	s	s	s
Pentachlorobenzene	i	s	ss	ss	ss
Hexachlorobenzene	i	ss	s	vs	s
Monobromobenzene	i	vs	vs	vs	—
1,2-Dibromobenzene	i	s	∞	∞	—
1,3-Dibromobenzene	i	s	∞	—	—
1,4-Dibromobenzene	i	s	vs	vs	—
1,2,3-Tribromobenzene	i	ss	vs	—	—
1,2,4-Tribromobenzene	i	s	vs	ss	—
1,3,5-Tribromobenzene	i	ss	s	s	s
1,2,3,4-Tetrabromobenzene	—	—	—	—	—
1,2,3,5-Tetrabromobenzene	i	s	s	s	—
1,2,4,5-Tetrabromobenzene	i	ss	vs	—	—
Pentabromobenzene	—	ss	ss	s	s
Hexabromobenzene	i	ss	ss	s	s
Monoiodobenzene	i	s	∞	∞	s
1,2-Diiodobenzene	ss	ss	vs	—	—
1,3-Diiodobenzene	i	s	s	—	s
1,4-Diiodobenzene	i	s	vs	—	—
1,2,3-Triiodobenzene	i	s	s	—	s
1,2,4-Triiodobenzene	i	s	s	—	s
1,3,5-Triiodobenzene	i	ss	ss	ss	ss
1,2,3,4-Tetraiodobenzene	—	vs	vs	—	vs
1,2,3,5-Tetraiodobenzene	i	ss	ss	—	—
1,2,4,5-Tetraiodobenzene	i	ss	ss	—	—
Pentaiodobenzene	i	ss	ss	s	s
Hexaiodobenzene	i	i	i	—	—
1-Bromo-2-chlorobenzene	i	—	—	vs	—
1-Bromo-3-chlorobenzene	i	vs	vs	—	—
1-Bromo-4-chlorobenzene	i	ss	s	s	s
1-Bromo-2,3-dichlorobenzene	i	ss	—	vs	—
1-Bromo-3,5-dichlorobenzene	i	s	s	vs	s
2-Bromo-1,3-dichlorobenzene	i	—	vs	vs	vs
2-Bromo-1,4-dichlorobenzene	i	s	vs	vs	vs
4-Bromo-1,2-dichlorobenzene	i	ss	vs	vs	vs
1-Bromo-4-fluorobenzene	i	s	s	—	—
1-Bromo-2-iodobenzene	i	ss	—	—	—
1-Bromo-3-iodobenzene	i	ss	—	—	—
1-Bromo-4-iodobenzene	i	ss	s	—	—
1-Chloro-2-fluorobenzene	i	—	—	s	—
1-Chloro-4-fluorobenzene	i	s	s	s	—
1-Chloro-2-iodobenzene	i	—	—	—	—
1-Chloro-3-iodobenzene	i	—	—	—	—
1-Chloro-4-iodobenzene	i	s	—	—	—
1-Fluoro-4-iodobenzene	i	s	s	—	—
1,4-Dichloro-2-iodobenzene	i	s	s	—	s

∞ - infinitely soluble
vs - very soluble
s - soluble
ss - slightly soluble
i - insoluble

TABLE 6

VAPOR PRESSURES OF HALOGENATED BENZENES
(Hardie, 1964; Richardson, 1968; Olin Chemicals, 1974)

Fluorinated Benzenes	Vapor Pressure (psig)
Monofluorobenzene	16.9 (Reid)
1,2-Difluorobenzene	16.7 (100°C)
1,3-Difluorobenzene	-
1,4-Difluorobenzene	17.15 (Reid)
1,2,3-Trifluorobenzene	-
1,2,4-Trifluorobenzene	-
1,3,5-Trifluorobenzene	$\log_{10}P(\text{torr}) = 6.9183 - \frac{1196.385}{t°C + 219.019}$ [at 6-50°C]
1,2,3,4-Tetrafluorobenzene	$\log_{10}P(\text{torr}) = 7.19386 - \frac{1396.067}{t°C + 228.73}$ [at 6-50°C]
1,2,3,5-Tetrafluorobenzene	$\log_{10}P(\text{torr}) = 7.07758 - \frac{1290.984}{t°C + 222.855}$ [at 6-50°C]
Pentafluorobenzene	$\log_{10}P(\text{mm}) = 6.94904 - \frac{1218.91}{t°C + 213.313}$ [at 19-85°C]
Hexafluorobenzene	$\log_{10}P(\text{torr}) = 6.86088 - \frac{1152.442}{t°C + 208.663}$

Chlorinated Benzenes	Vapor Pressure (mm/Hg at 25°C unless otherwise indicated)
Monochlorobenzene	3(0°C), 9(20°C), 26(40°C), 65(60°C) 144(80°C), 292(100°C), 543(120°C)
1,2-Dichlorobenzene	1.28
1,3-Dichlorobenzene	1.89
1,4-Dichlorobenzene	0.4(25°C), 6.6(50°C), 11.5(60°C), 67(100°C), 545(160°C)
1,2,3-Trichlorobenzene	0.07
1,2,4-Trichlorobenzene	0.29
1,3,5-Trichlorobenzene	0.15
1,2,3,4-Tetrachlorobenzene	-
1,2,3,5-Tetrachlorobenzene	-
1,2,4,5-Tetrachlorobenzene	0.05
Pentachlorobenzene	-
Hexachlorobenzene	1.09×10^{-5} (at 20°C)

The three difluorobenzene isomers are colorless, neutral liquids at room temperature. Like monofluorobenzene, they are highly flammable and have low flash points. Very little solubility data was found for fluorinated benzenes. The tendency is towards insolubility in water and solubility in nonpolar solvents.

Ortho- and meta-dichlorobenzene are neutral, mobile, colorless liquids with similar and characteristic odors. p-Dichlorobenzene is a pleasant smelling white crystalline solid. The crystals readily sublime at room temperature. Solubilities of the dichlorobenzenes are similar to MCB, and like the monocompound, they form a number of azeotropic mixtures (Hardie, 1964). All three are combustible. Additional data on physical properties are found in Tables 2 and 5.

Like the dichlorobenzene compounds, o- and m-dibromobenzene are colorless liquids at room temperature. p-Dibromobenzene is a white crystalline solid. All dibromobenzenes are insoluble in water, soluble in alcohol and infinitely soluble in ether. The diiodobenzenes are all crystalline solids. o-Diiodobenzene is slightly soluble in water and all diiodobenzenes are soluble in non-polar solvents.

The trihalogenated benzenes are white crystalline solids except for the trifluorobenzenes and the 1,2,4-trichlorobenzene isomer. Solubilities are similar, with insolubility in water, generally good solubility in alcohol, ether, benzene and chloroform, and relatively high lipid solubility.

All the polyfluorinated compounds are colorless liquids. Tetra-, penta- and hexachlorobenzene are white crystalline solids at room temperature. The polybromo- and polyiodobenzene compounds are white crystalline solids which tend to sublime.

TABLE 7

AZEOTROPIC MIXTURES OF CHLOROBENZENE
(Hardie, 1964)

Other Components	Boiling Point of Azeotrope, (°C)	Chlorobenzene % by wt.	Water % by wt.	Hydrogen chloride % by wt.
Binary:				
water	90.2	71.6	28.4	
1-amino-2-propanol	128.3	87.0		
3-methyl-1-butanol (isoamyl alcohol)				
2-methyl-1-butanol (_d_-amyl alcohol)	124.4	57		
_n_-propanol	96.5	20.0		
Ternary:				
hydrogen chloride and water	96.9	74.5	20.2	5.3

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TABLE 8

FIRE AND EXPLOSION HAZARD DATA FOR SOME HALOGENATED BENZENES
(Montrose Chemical Corp., 1972; Olin Chemicals, 1974; Great Lakes Chemical Corp., 1975; Merck, 1976; Dow Chemical, 1977b)

Compound	Flash point (°F)	Flash point (°C)	Method Used	Flammable Limits (STP in air) Lower	Flammable Limits (STP in air) Upper
Fluorobenzene	9°	-12.8°	Open cup	-	-
1,2-Difluorobenzene	45°	7.2°	Open cup	-	-
1,3-Difluorobenzene	12°	-11.1°	Open cup	-	-
1,4-Difluorobenzene	11°	-11.7°	Open cup	-	-
Monochlorobenzene	82°	27.8°	Closed cup	1.3%	7.1%
1,2-Dichlorobenzene	160°	71.1°	Closed cup	2.2%	9.2%
1,4-Dichlorobenzene	152°	66.7°	Closed cup	-	-
1,2,3-Trichlorobenzene	235°	112.8°	Closed cup	-	-
1,2,4-Trichlorobenzene	210°	98.9°	Closed cup	(none at 25°C)	
1,3,5-Trichlorobenzene	225°	107.2°	Closed cup	-	-
1,2,4,5-Tetra-chlorobenzene	311°	155.0°	Closed cup	-	-
Hexachlorobenzene	468°	242.2°	Closed cup	-	-

Solubility tends to be lower in all solvents for the hexahalobenzene compounds. Hexaiodobenzene is insoluble in water, alcohol, and ether, while hexabromobenzene is insoluble in water, and only slightly soluble in chloroform. Hexachlorobenzene is insoluble in water and only slightly soluble in alcohol and ether. There is a tendency for tetra- and pentahalogenated benzenes to be slightly less soluble in alcohol than the lower homologues. Polyiodinated benzenes as a group are less soluble in alcohol, ether, benzene and chloroform than are the corresponding chloro- and bromo- compounds. All halogenated benzenes have high lipid solubility.

While fluorinated benzenes and the lower chlorinated and brominated compounds tend to be flammable or combustible liquids, higher brominated benzenes have been used as fire-retardant materials, and some higher chlorinated benzenes have been suggested for this use.

Several chlorinated benzenes are used for heat transfer or as dielectric fluids in transformers and capacitors. Properties important for such uses include: chemical stability, value of the dielectric constant, viscosity, surface tension and thermal conductivity. Values are listed in Table 9.

4. Physical Properties and Contaminants of the Commercial Material

No specific data is recorded in this section. It might be noted that contaminants of the commercially available materials are either other isomers or homologues (see Table 10).

As solvent properties of the mixtures tend to be close to those of the pure products, for solvent uses, it often does not matter if the compound is pure or not.

TABLE 9

ADDITIONAL PROPERTIES OF CHLORINATED BENZENES
(Dow Chemical, 1970, 1972)

Compound	Dielectric Constant (25°C)	Surface Tension (dynes/cm. 25°C)	Thermal Conductivity* (25°C)	Viscosity (cp) (25°C)
Monochlorobenzene	5.621	32.65	3.038 -4	0.756
1,2-Dichlorobenzene	9.93	36.61	2.878 -4	1.3018
1,4-Dichlorobenzene	2.41 [50°]	31.4 [60°] 27.2 [100°]	3.08 -4 2.58 -4 [60°]	-
1,2,4-Trichlorobenzene	2.24 [20°]	38.54	2.582 -4 [28°]	1.8848

* in $\frac{\text{cal}}{\text{sec cm}^2(°\text{C/cm})}$

TABLE 10

REPRESENTATIVE ANALYSES OF COMMERCIALLY IMPORTANT CHLORINATED BENZENES

(Dow Chemical, 1970; Montrose Chemical Corp., 1972; Allied Chemical, 1973; Manufacturing Chemists Association, 1974; Great Lakes Chemical Corp., 1975)

Chemical	%	Mono-chlorobenzene	1,2-Di-chlorobenzene	1,3-Di-chlorobenzene	1,4-Di-chlorobenzene	Impurities		Penta-chlorobenzene	Hexa-chlorobenzene	Water	Color (APHA)
						Tri-chlorobenzene	Tetra-chlorobenzene				
Monochlorobenzene	99.9		x		x						
	90		x		x					47ppm	2.5
1,2-Dichlorobenzene	99			x	x					x	
	75-85	x		0-5	15-25	x				x	
	82.7	0.07		0.5	15.4	x				x	
	80	x		2	17	1.6				x	
	60-75	x		x	25-40	x				x	
1,4-Dichlorobenzene	99.95		x			x					
	99.5	x	x	x							
	96	x	x	x							
	65	x	35	x							
1,2,4-Trichlorobenzene	100					*					
	99					x					
1,2,4,5-Tetrachlorobenzene	97					x	*	x			
Pentachlorobenzene	-						x		x		
Hexachlorobenzene	90-99						x	9%			

* other isomers

5. Chemical Properties

(a) General Discussion

Phenyl halides are much less reactive than the corresponding alkyl compounds, and are similar in reactivity to the vinyl halides. They are very stable to nucleophilic attack — a fact attributed to resonance in the molecule resulting in shortening of the carbon-halogen bond distance, and hence an increase in bond strength (Fieser and Fieser, 1960).

At room temperature and pressure, halogenated benzenes are not attacked by air, moisture or light. They are not affected by steam, prolonged boiling with aqueous or alcoholic ammonia, other alkalis, hydrochloric acid or dilute sulfuric acid. Hydrolysis takes place at elevated temperatures in the presence of a catalyst to form phenols.

Halogenated benzenes are subject to attack by hot concentrated sulfuric acid to form a halobenzene-p-sulfonic acid. Nitric acid will substitute m-, p- in the ring to form halonitrobenzenes at -30° to 0°C. At higher temperatures, the nitration will either proceed further to form a dinitrohalo compound, a halonitrophenol or a nitrophenol.

The stability of halogenated benzenes to nucleophilic attack decreases in the order $F > Cl > Br > I$. Additional substitution in the ring activates the nucleus to nucleophilic attack. Hence, polyhalogenated benzenes are more susceptible to nucleophiles because of the electron attractive ($I\sigma$) effect of the substituents. Nucleophilic attack is also possible in the presence of a catalyst (often a cuprous salt) and at elevated temperatures and pressures.

Halogenated benzenes are attacked by electrophilic agents. Here the order of reactivity is greatest for the fluorine compounds decreasing toward the iodobenzenes. Substitution for mono compounds is predominantly para, with some ortho substitution. The higher halogenated benzenes tend to resist electrophilic substitution but can be substituted using extreme conditions. For example, Friedel-Crafts alkylation of pentafluorobenzene occurs under autogenous pressure at 150°C (Feast and Musgrave, 1971).

Halogenated benzenes also undergo some free radical reactions. Formation of organometallic compounds (Grignards, aryl-lithium compounds) provides a useful route to many organic intermediates (see Section IIB).

Photochemical transformations occur on irradiation of halogenated benzenes which are much less stable to radiation than benzene. On ultraviolet irradiation or pulse hydrolysis in solution, halogenated benzenes may polymerize to biphenyls, halonapthalenes, or other more complex products (Matsuura and Omura, 1966; MacKenzie et al., 1965; MacLachlan and McCarthy, 1962).

Photochemical interchange of halogens is also possible:

$$ArX + X' \longrightarrow ArX' + X$$

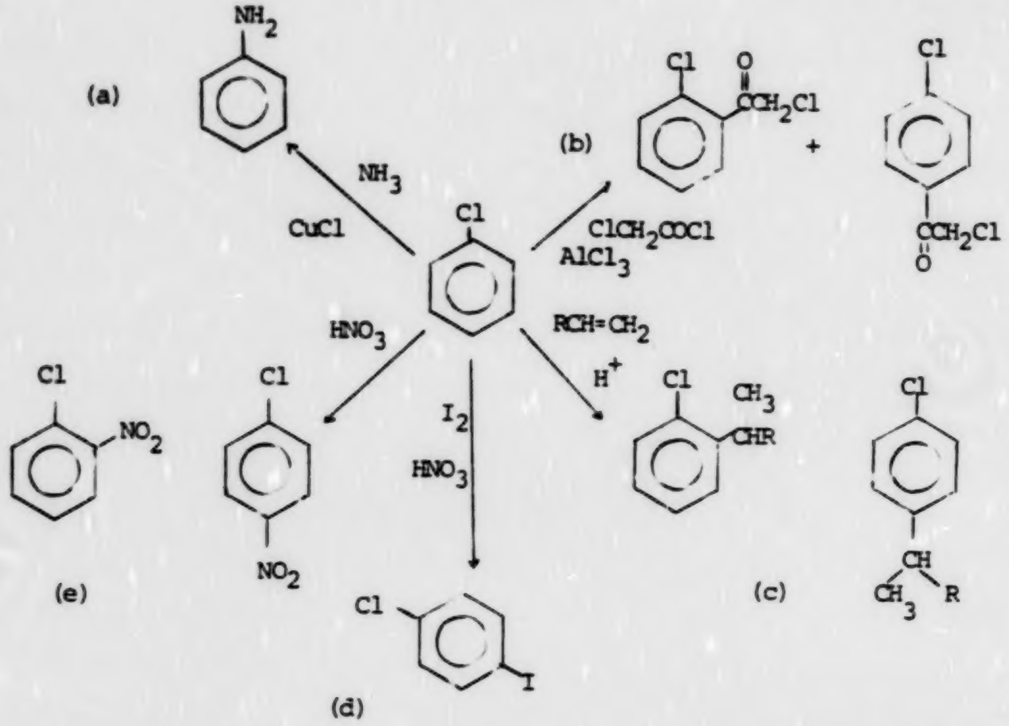
Here, bromine replaces iodine in iodobenzenes, chlorine replaces bromine or iodine, etc. Echols et al. (1967) have shown that the rate of the photochemical reaction $2PhBr + Cl_2 \longrightarrow 2PhCl + Br_2$ in carbon tetrachloride solution is proportional to the square root of the light intensity, halogen concentration and to the bromobenzene concentration over a limited range.

(b) Chemical Reactions Involved in Use

Chemical reactions involved in use are discussed in detail in Section IIB. Figures 2, 3, 4 and 5 summarize possible reactions for the commercially important chlorinated benzenes, and serve as an introduction to the following section. The nitration reaction is the single most important industrial reaction. The reactions diagrammed in Figures 2-5 are not necessarily industrially significant, but are examples of possible reactions.

FIGURE 2 REACTIONS INVOLVED IN USE OF CHLOROBENZENE

(Dow Chemical, 1975b)



(a)
NH_2
NH_3
CuCl
Cl
(b)
Cl
O
CCH_2Cl
+
Cl
CCH_2Cl
O
$ClCH_2COCl$
$AlCl_3$
HNO_3
$RCH=CH_2$
H^+
Cl
NO_2
Cl
NO_2
I_2
HNO_3
Cl
CH_3
CHR
Cl
CH
CH_3
R
(e)
(c)
Cl
I
(d)

(a) Catalytic addition of ammonia to form aniline, high temperature and pressure

(b) Friedel-Crafts arylating agent in presence of a Lewis acid

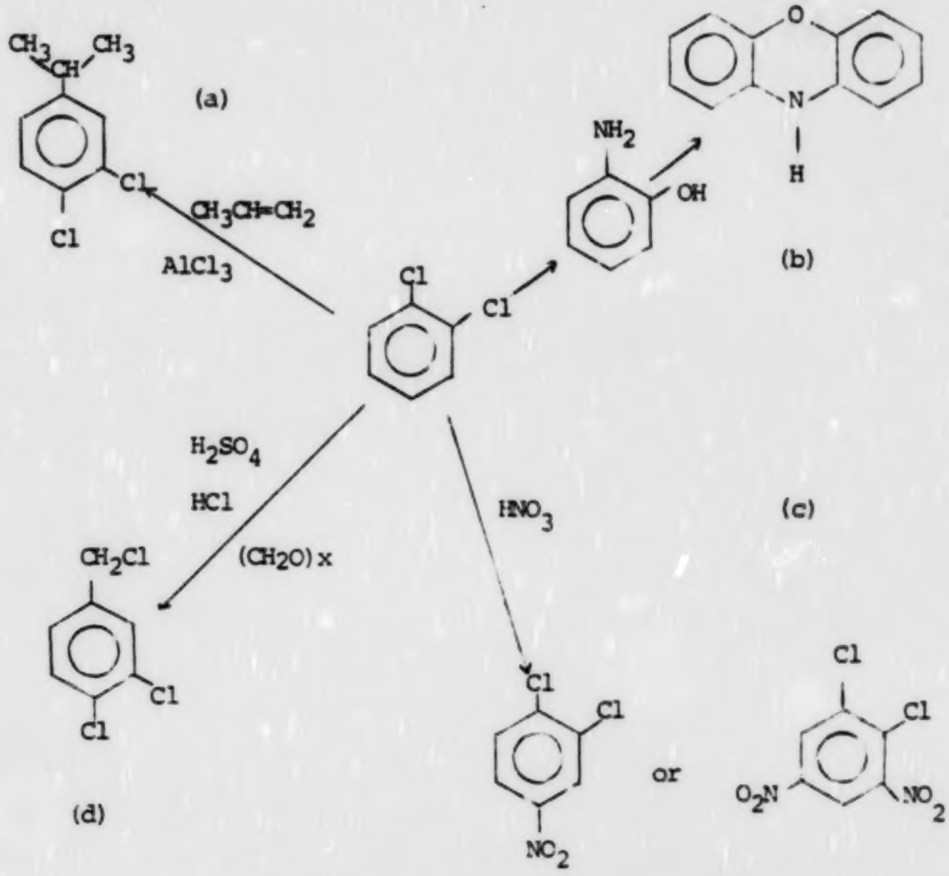
(c) Acid catalyzed addition of an olefinic grouping

(d) Oxidative iodination to p-chloroiodobenzene

(e) Ring substitution, here to o- and p-chloronitrobenzene

FIGURE 3 REACTIONS INVOLVED IN USE OF 1,2-DICHLOROBENZENE (ODCB)

(Dow Chemical, 1975b)



(a)
$CH_3CH=CH_2$
$AlCl_3$
(b)
(c)
H_2SO_4
HCl
$(CH_2O)x$
HNO_3
(d)
or

(a) Friedel-Crafts alkylation in fifth position

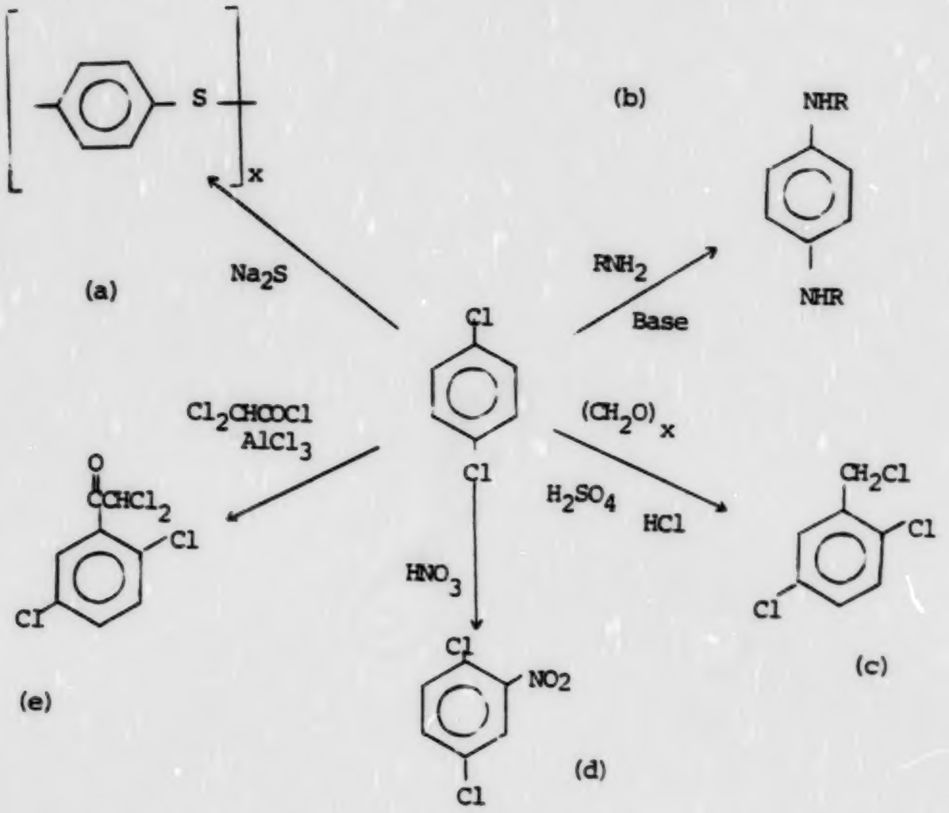
(b) Reaction of o-aminophenol with a base results in formation of phenoxazine

(c) Ready aromatic substitution- nitric acid to nitro- and dinitro- compounds

(d) Acid catalyzed substitution in fifth position

FIGURE 4 REACTIONS INVOLVED IN USE OF 1,4-DICHLOROBENZENE

(Dow Chemical, 1975b)



S
x
(a)
Na2S
(b)
NHR
RNH2
Base
NHR
Cl
Cl2CHCOCl
AlCl3
(CH2O)x
Cl
O
CCHCl2
Cl
Cl
H2SO4
HCl
CH2Cl
Cl
Cl
HNO3
Cl
NO2
(e)
(c)
(d)
Cl

(a) Linear polymers such as polyphenylene sulfide can be formed, Wurtz-Fittig reaction also used

(b) For example, aqueous ammonia and cupric oxide catalyst produce p-phenylene diamine

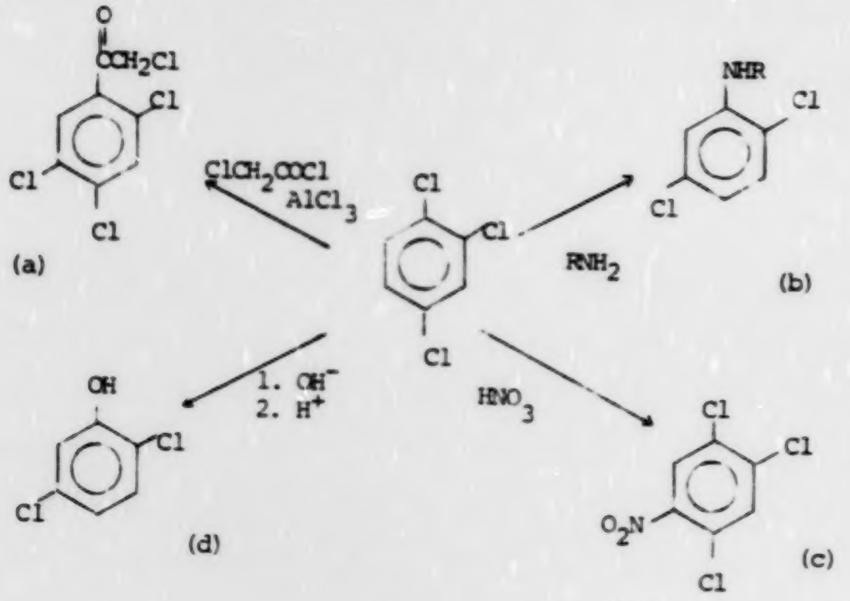
(c) Acid catalyzed substitution

(d) Readily nitrated in 1-position

(e) Friedel-Crafts addition of an acid chloride, also with alkenes and alkyl halides.

FIGURE 5 REACTIONS INVOLVED IN USE OF 1,2,4-TRICHLOROBENZENE

(Dow Chemical, 1975b)


O
CCH2Cl
Cl
Cl
Cl
(a)
ClCH2COCl
AlCl3
Cl
Cl
Cl
NHR
Cl
Cl
RNH2
(b)
OH
1. OH⁻
2. H⁺
Cl
Cl
(d)
HNO3
Cl
Cl
O2N
Cl
(c)

(a) Mild Friedel-Crafts conditions: alkylation and acylation in fifth position

(b) Catalyzed reaction with primary amine to form a dichlorinated secondary amine

(c) Nitration of ring in fifth position

(d) Alkaline hydrolysis to 2,5-dichlorophenol

Also note, 2,5-dichlorobenzoic acid is formed by cyanation followed by hydrolysis of 1,2,4-trichlorobenzene.

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II. ENVIRONMENTAL EXPOSURE FACTORS

A. PRODUCTION AND CONSUMPTION

(a) CHLORINATED BENZENES

1. Quantity Produced, Market Trends, Market Prices

Chlorobenzene was first produced in the United States by the Dow Chemical Company in 1915 (Hardie, 1964). It was one of the first organic chemicals produced in large quantities. U.S. production figures are available through the U.S. International Trade Commission reports published since 1922. The U.S. International Trade Commission (USTIC) was formerly the U.S. Trade Commission (USTC). Table 11 documents production and sales figures for the ten year period 1966 to 1975. As can be clearly seen in Figure 6, monochlorobenzene production has been on the decrease since 1969, dropping to around 300 million pounds production in 1975. The low figure for 1974 is attributed to long strikes at Dow Chemical and PPG Industries, and to a shortage of benzene early in the year (Chemical Marketing Reporter, 1974a). Preliminary figures for 1976 are also down — the nine month accumulative figures from January to September show production of 252,078 x 10^3 pounds.

Tables 12 and 13, and Figure 7 illustrate market trends for *o*- and *p*-dichlorobenzene over the last ten years. Preliminary figures for 1975 show a decreased production of *o*-dichlorobenzene to about 54 to 55 million pounds. Nevertheless, future markets for ODCB look promising, and the industry expects the demand for this isomer to increase (Chemical Marketing Reporter, 1975). The versatility of ODCB as a solvent accounts for its expanding markets. Preliminary figures for 1975 indicate a decrease in production of *p*-dichlorobenzene to 40 million pounds. The market for the *para* isomer is limited by the possible uses of the chemical, and is considered saturated.

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Tables 12 and 13, and Figure 7 illustrate market trends for o- and p-dichlorobenzene over the last ten years. Preliminary figures for 1975 show a decreased production of o-dichlorobenzene to about 54 to 55 million pounds. Nevertheless, future markets for ODCB look promising, and the industry expects the demand for this isomer to increase (Chemical Marketing Reporter, 1975). The versatility of ODCB as a solvent accounts for its expanding markets. Preliminary figures for 1975 indicate a decrease in production of p-dichlorobenzene to 40 million pounds. The market for the para isomer is limited by the possible uses of the chemical, and is considered saturated.

TABLE 11

U.S. PRODUCTION OF MONOCHLOROBENZENE, 1966-1975
(USITC, 1966a-1975a)

		Sales		
Year	Production (10^3 lbs.)	Quantity (10^3 lbs.)	Total Value ($\$10^3$)	Unit Value ($/lb.)
1966	576,749	130,570	7,795	0.06
1967	483,294	67,857	4,145	0.06
1968	575,751	142,654	8,501	0.06
1969	601,959	93,164	5,231	0.06
1970	484,914	66,755	3,699	0.06
1971	408,908	71,475	3,779	0.05
1972	403,505	85,244	4,817	0.06
1973	397,481	125,735	8,237	0.07
1974	379,181	71,683	15,312	0.214
1975*	306,030	77,363	20,410	0.25
1955	435,593	55,195	4,412	0.08
1956	452,434	68,444	5,127	0.07

* Preliminary figures

Please note that weights are expressed in pounds (avdp.) as is customary in this country. 10^3 pounds = 0.454 metric ton, 1 pound = 0.454 kg.

TABLE 12

U.S. PRODUCTION OF O-DICHLOROBENZENE, 1966-1975
(USITC, 1966a-1975a)

Year	Production	Sales		
	(10^3 lbs.)	Quantity (10^3 lbs.)	Total Value ($\$10^3$)	Unit Value ($/lb.)
1966	51,386	50,726	5,065	0.10
1967	50,366	45,970	4,721	0.10
1968	60,603	46,290	4,977	0.11
1969	70,372	53,027	5,532	0.10
1970	66,219	35,074	3,503	0.10
1971	53,640	55,935	5,829	0.10
1972	62,386	62,389	7,233	0.12
1973	66,035	67,055	8,659	0.13
1974	n.a.	n.a.	n.a.	n.a.
1975*	54,679	50,456	13,960	0.28

* Preliminary figures

TABLE 13

U.S. PRODUCTION OF P-DICHLOROBENZENE, 1966-1975
(USITC, 1966a-1975a)

Year	Production	Sales		
	(10^3 lbs.)	Quantity (10^3 lbs.)	Total Value ($\$10^3$)	Unit Value ($/lb.)
1966	66,307	65,659	5,893	0.09
1967	66,482	64,719	5,782	0.09
1968	70,338	69,117	6,646	0.10
1969	52,060	53,934	4,991	0.09
1970	69,606	69,669	6,165	0.09
1971	70,418	69,187	5,805	0.08
1972	77,317	70,704	6,285	0.09
1973	62,743	69,398	6,436	0.09
1974	n.a.	n.a.	n.a.	n.a.
1975*	45,755	34,099	8,371	0.25

* Preliminary figures

FIGURE 6 U.S. PRODUCTION OF MONOCHLOROBENZENE, 1966-1975
(USITC 1966a-1975a)

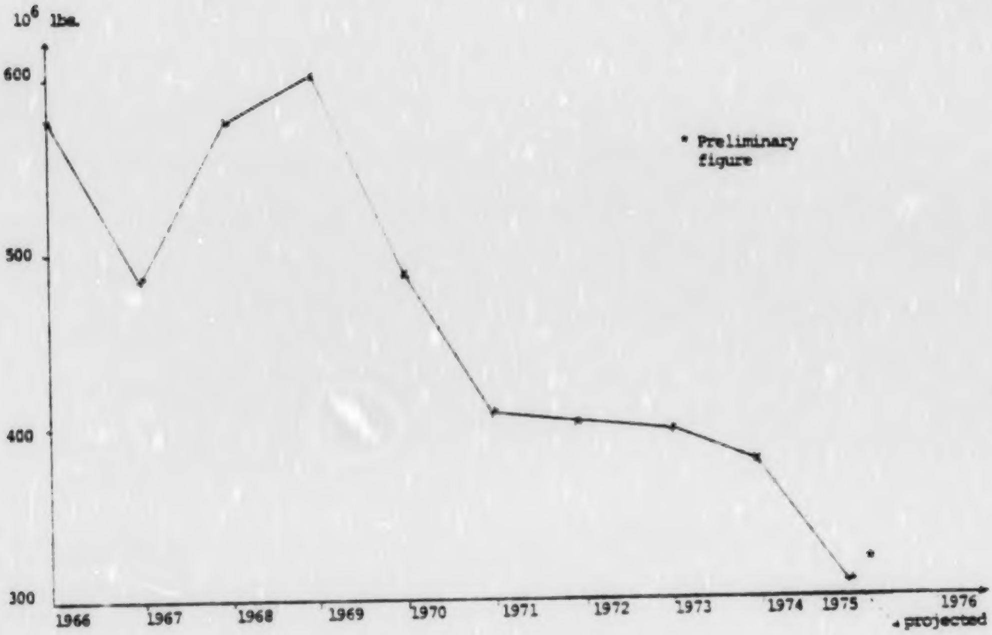
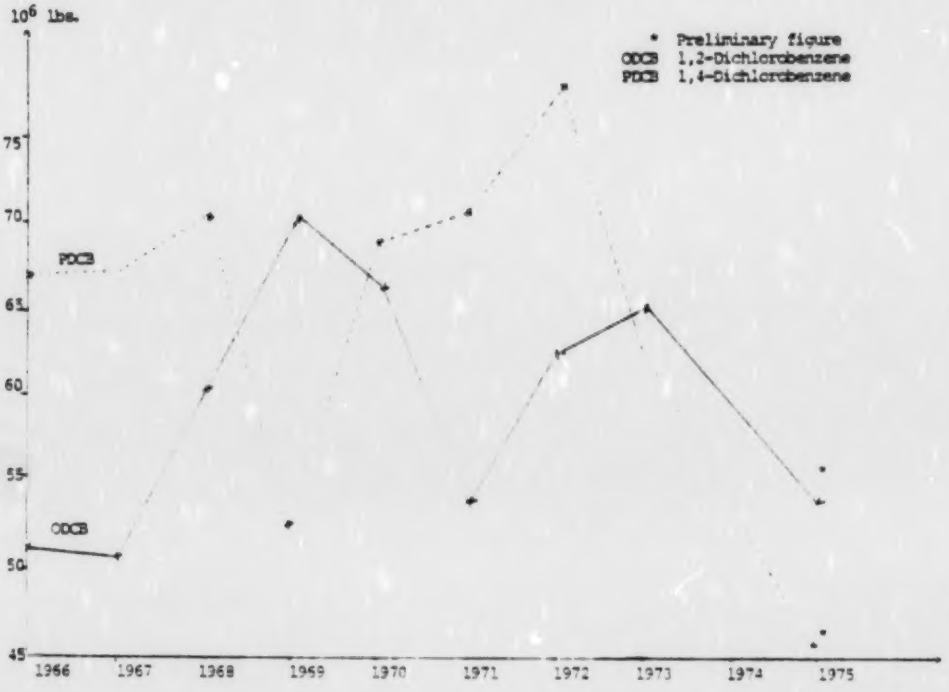


FIGURE 7 U.S. PRODUCTION OF DICHLOROBENZENES
(USITC, 1966a-1975a)



In 1973, production of 1,2,4-trichlorobenzene was 28,268 x 10^3 pounds. Table 14 gives production and sales data for trichlorobenzene from 1968 to 1973. In 1973, production of 1,2,4,5-tetrachlorobenzene was estimated at 18 million pounds (Lewis, 1975). Pentachlorobenzene production for commercial sales was estimated at less than 1 ton in 1972 (Mumma and Lawless, 1975). Figures for captive production were not available. The estimated total production of hexachlorobenzene was 350 tons in 1973 (Mumma and Lawless, 1975).

TABLE 14

U.S. PRODUCTION OF 1,2,4-TRICHLOROBENZENE, 1968-1973
(USITC, 1968a-1973a)

Year	Production (10^3 lbs.)	Sales Quantity (10^3 lbs.)	Sales Total Value ($\$10^3$)	Sales Unit Value ($/lb.)
1968	10,867	11,069	1,295	0.12
1969	15,217	13,329	1,564	0.12
1970	9,344	9,531	1,185	0.12
1971	11,034	12,130	1,361	0.11
1972	15,522	15,667	2,020	0.13
1973	28,268	26,198	3,607	0.14

As explained below, higher chlorinated benzenes are coproduced with the monosubstituted compound in varying proportions, depending on reaction conditions. The Dow Chemical Company is replacing and expanding its chlorinated benzene production machinery in Midland, Michigan. The plant is capable of manufacturing approximately 300 to 350 million pounds of chlorobenzene per year, much of which is converted to phenol. Some of the MCB goes to produce o- and p-dichlorobenzene, trichlorobenzene and tetrachlorobenzene. It has been estimated (Chemical Marketing Reporter, 1975) that about 22 million pounds of the monochlorobenzene goes to o-dichlorobenzene production and 16 million pounds to production of the para isomer. Dow technology is being altered to produce higher chlorobenzenes and to permit greater flexibility in production. Over the long term, Dow intends to phase out phenol production via monochlorobenzene in favor of phenol production at its cumene-based plant in Oyster Creek, Texas.

Please note, USITC does not have figures for production of 1,2,4-trichlorobenzene for 1974 or 1975. This is presumably because the chemical is produced by only a few manufacturers and publication of data would reveal proprietary information.

USITC reports do not give any figures for production of other chlorinated (or other halogenated) benzenes. This is also presumably either because of monopolies or near-monopolies of manufacture and/or because the chemicals are not produced in great enough quantities to warrant entry in the Federal government reports. The criteria for inclusion require that the chemical be produced in excess of 1,000 pounds/annum or have a value of at least $1,000. Some indication of importance of specific chemicals can be deduced from Section IIB below. Lewis (1975) reported 1973 production of 1,2,4,5-tetrachlorobenzene of 18 million pounds.

Import data for several of the chlorinated benzenes are found in Table 15. Principal chlorobenzene-producing countries include West Germany, the United Kingdom, France and Japan (Hardie, 1964). In 1974, imports of 1,2,4-trichlorobenzene in to the U.S. exceeded 2 million pounds (USITC 1974b). The chief exporting nations were Belgium, France and West Germany.

With reference to the completeness of Table 15, it should be noted that for benzenoid intermediates, the data collected by the U.S. International Trade Commission are reported to be 99% complete (USITC 1974b). Carry-over of year end entries to the following year tends to be reasonably constant from year to year. Hence, though year-to-year comparisons are possible for chemicals imported on a regular basis, for chemicals imported irregularly, there is some statistical distortion.

TABLE 15

U.S. IMPORTS OF CHLORINATED BENZENES, 1971-1974
(USITC, 1971b-1974b)

Product	1971 (lbs.)	1972 (lbs.)	1973 (lbs.)	1974 (lbs.)
Monochlorobenzene	*	*	*	1,485,106
o-Dichlorobenzene	*	13,800	*	1,631,404
m-Dichlorobenzene	*	*	2,191	31,006
p-Dichlorobenzene	*	*	3,527	*
Trichlorobenzene (mixed isomers)	*	*	*	940,715
1,2,4-Trichlorobenzene	*	*	*	2,770,245
1,3,5-Trichlorobenzene	*	2,870	45,492	21,525
1,2,4,5-Tetrachlorobenzene	*	*	167,551	1,467,819

* Note: no information given for these chemicals

2. Producers, Processors and Production Sites

Dow Chemical Company, the Monsanto Company, PPG Industries, the Montrose Chemical Corporation of California and the Standard Chlorine Chemical Company are the largest producers of monochlorobenzene in the U.S. ICC Solvent Company, Inc. and Allied Chemical Corporation also manufacture monochlorobenzene. Annual manufacturing capacity of the individual companies is indicated in Table 16. Dow Chemical has an annual capacity of 300 to 350 million pounds at its Midland, Michigan, plant. As previously indicated, Dow Chemical is adapting its plant to produce higher chlorinated benzenes in greater quantities. The Monsanto Company has an annual capacity of about 125 million pounds at its Sauget, Illinois, facility. Both PPG Industries and Standard Chlorine completed expansions of their plants in 1974 and are planning further new units for the near future (Chemical Marketing Reporter, 1975).

The same companies produce the bulk of o- and p-dichlorobenzene (see Table 16). A complete tabulation of all companies listed by USITC as manufacturers is given in Table 17. All manufacturers listed in the 1975 Stanford Research Institute (SRI) directory for 1976 were contacted for verification of their status as producers or major processors. One firm, Transvaal, Inc., indicated that it no longer produces tetrachlorobenzene, but finds it cheaper to import the chemical (Transvaal Inc., 1976). The first shipment is now on order from West Germany.

In general, producers manufacture a range of chlorinated benzenes. Each plant therefore has the flexibility to produce more or less of a particular chemical depending on market demand. Processors buy mixtures of chlorobenzenes to separate and upgrade the mixture by fractional distillation (e.g., Specialty Organics).

TABLE 16
CHLORINATED BENZENES, CAPACITIES* IN MILLIONS OF POUNDS/YEAR
(Lewis, 1975)

Producer	Mono-chlorobenzene	Dichloro-benzene (o- and p-)	Trichloro-benzene (1,2,4-)
Allied Chemical Corp., Industrial Chemicals Div.	20	22	-
Dow Chemical, USA.	350	40	10
Monsanto Company, Industrial Chem. Div.	125	12	not recovered
Montrose Chemical Corp. of California	70	5	-
Occidental Petroleum Corp. Hooker Chems. and † Plastics Corp.	-	-	7
PPG Inc. Industrial Chems. Div.	30	40	-
ICC Industries, Inc. Solvent Chemical Company			
(a) Malden, Mass. ‡	-		n.a.
(b) Niagara Falls, N.Y.	-	(10)	n.a.
Standard Chlorine Chem. Co.	75	75	18
Total	670	204	35

---

* Many capacities believed understated. List partially outdated by expansions of PPG Industries to 135 million pounds by end of 1975. Further expansion of PPG Industries Natrium facility is increasing production to 300 million pounds (Chemical Marketing Reporter, 1974b).

† Hooker Chemical Corp. no longer produces any chlorinated benzenes.

‡ Malden plant phasing out. Production now centered at Niagara Falls.

TABLE 17

U.S. PRODUCERS OF CHLORINATED BENZENES

	Monochloro-benzene	o-Dichloro-benzene	m-Dichloro-benzene	p-Dichloro-benzene	1,2,3-Tri-chlorobenzene	1,2,4-Tri-chlorobenzene	1,3,5-Tri-chlorobenzene	1,2,3,4-Tetra-chlorobenzene	1,2,3,5-Tetra-chlorobenzene	1,2,4,5-Tetra-chlorobenzene	Pentachloro-benzene	Hexachloro-benzene
Allied Chem. Corp.	▲ o	▲ o		▲ o								
Dow Chem. Co.	▲ o	▲ o		▲ o	▲	o				▲ o	4	
ICC-Solvent Chem. Co.	o	o	o			o					4	
Monsanto Co.	▲ o	▲ o		▲ o								
Montrose Chem. Corp. of Calif.	▲ o	▲ o		▲ o								
Hooker Chem. & Plastics Co. 3	o				▲	o					4	
PPG Indust. Inc.	▲ o	▲ o		▲ o	▲							
Standard Chlorine	o	o		o								
Dover Chemical Corp.				▲							4	▲ o
Chemical Products Corp. 1,3		o										
Specialty Organics 1		o		o								
Eastman Kodak			o									
Guardian Chem. Co.			o									
Transvaal, Inc. 2								o		o		
Aceto Chemical Co.											*	
Chem. Procurement Labs. Inc.											*	
Stauffer Chem. Co.												*

Key

1	Processor
2	Transvaal, Inc. no longer runs unit, cheaper to import (Transvaal, Inc., 1976)
3	No longer produce or process
4	Captive by-product (Mumma and Lawless, 1975)
▲	U.S. International Trade Commission,1975a
o	Stanford Research Institute, 1975a, 1976
*	Mumma and Lawless, 1975

Table 18 and Figure 8 give the manufacturing sites for chlorinated benzene production. To clarify the map, seven of the sites pinpointed make three or more chlorinated benzenes, i.e. usually monochlorobenzene, *o*- and *p*-dichlorobenzene and trichlorobenzenes. Those sites where production is greatest are indicated by the dark circle.

Three other facilities are identified on the map by a solid triangle. These plants are smaller, and are indicated in Table 17 as manufacturing two or less of the chemicals.

3. Production Methods and Processes

Chlorobenzene and higher chlorinated benzenes are produced when benzene reacts with chlorine at slightly elevated temperatures in the presence of various catalysts. The reaction is exothermic.

$$C_6H_6 + Cl_2 \longrightarrow C_6H_5Cl + HCl \qquad + 40\ \text{k.cal}$$

$$C_6F_5Cl + Cl_2 \longrightarrow C_6H_4Cl_2 + HCl$$

After one chlorine has substituted onto the benzene ring, further substitution takes place principally in the *ortho* and *para* positions. All three dichlorobenzenes yield a preponderant amount of 1,2,4-trichlorobenzene on further chlorination. The rate of substitution decreases with degree of chlorination (Hardie, 1964). Because of the slowness of reaction and the strong directing effect of previous substitution, some isomers must be prepared by other routes (see below).

TABLE 18

LOCATIONS OF PRODUCTION SITES
(USITC, 1974a; Lewis, 1975)

Company	Division	Location
Allied Chemical Corp.	Industrial Chemicals Division	Syracuse, N.Y.
Dow Chemical, U.S.A.		Midland, Michigan
Monsanto Company	Industrial Chemicals Division	Sauget, Illinois
Montrose Chemical Corp. of California		Henderson, Nevada
PPG Industries, Inc.	Industrial Chemicals Division	Natrium, W. Virginia
Standard Chlorine Chemical Co., Inc.		Delaware City, Delaware
ICC Industries, Inc.	Solvent Chemical Company	Malden, Mass* Niagara Falls, New York

*Phasing out production

FIGURE 8 U.S. PRODUCTION SITES FOR THE CHLORINATED BENZENES

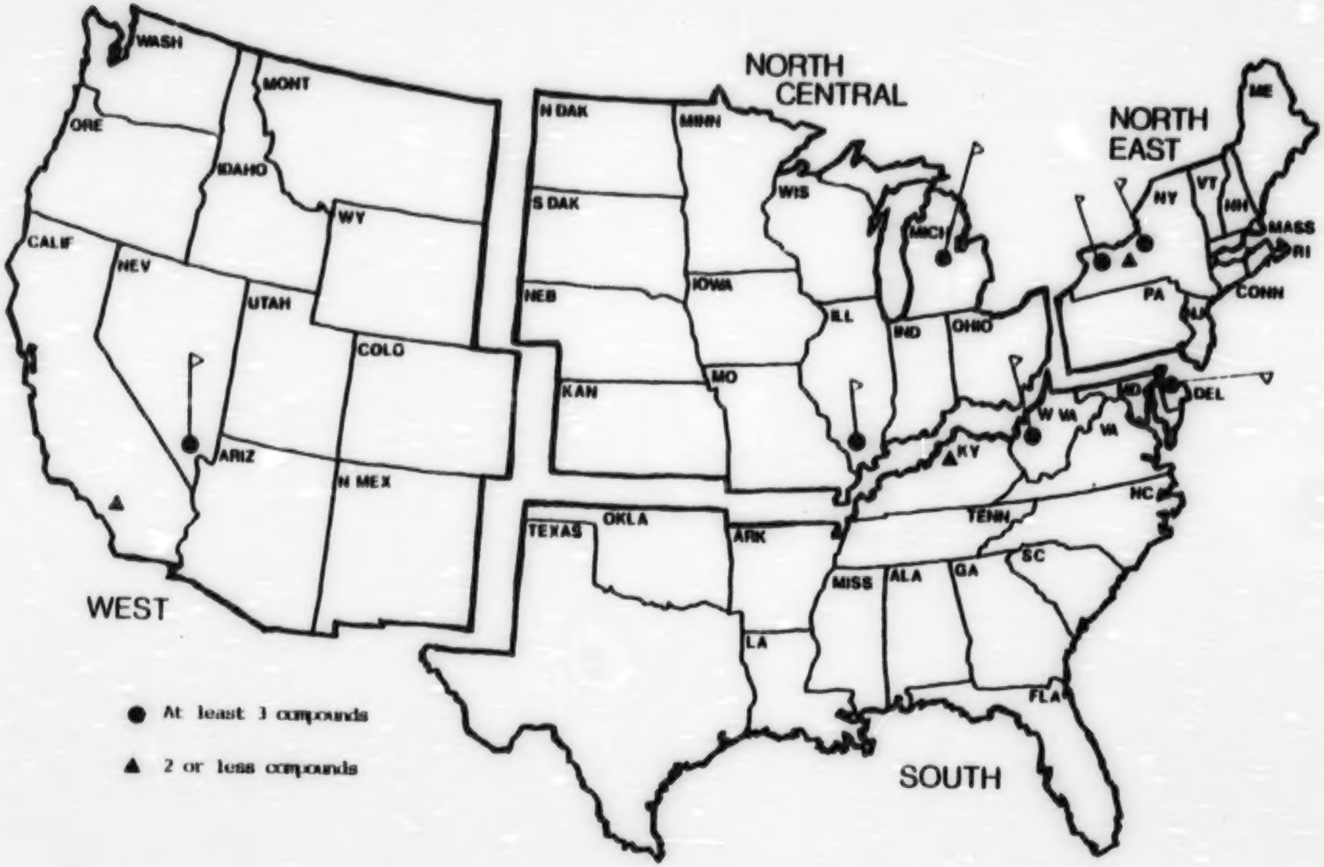
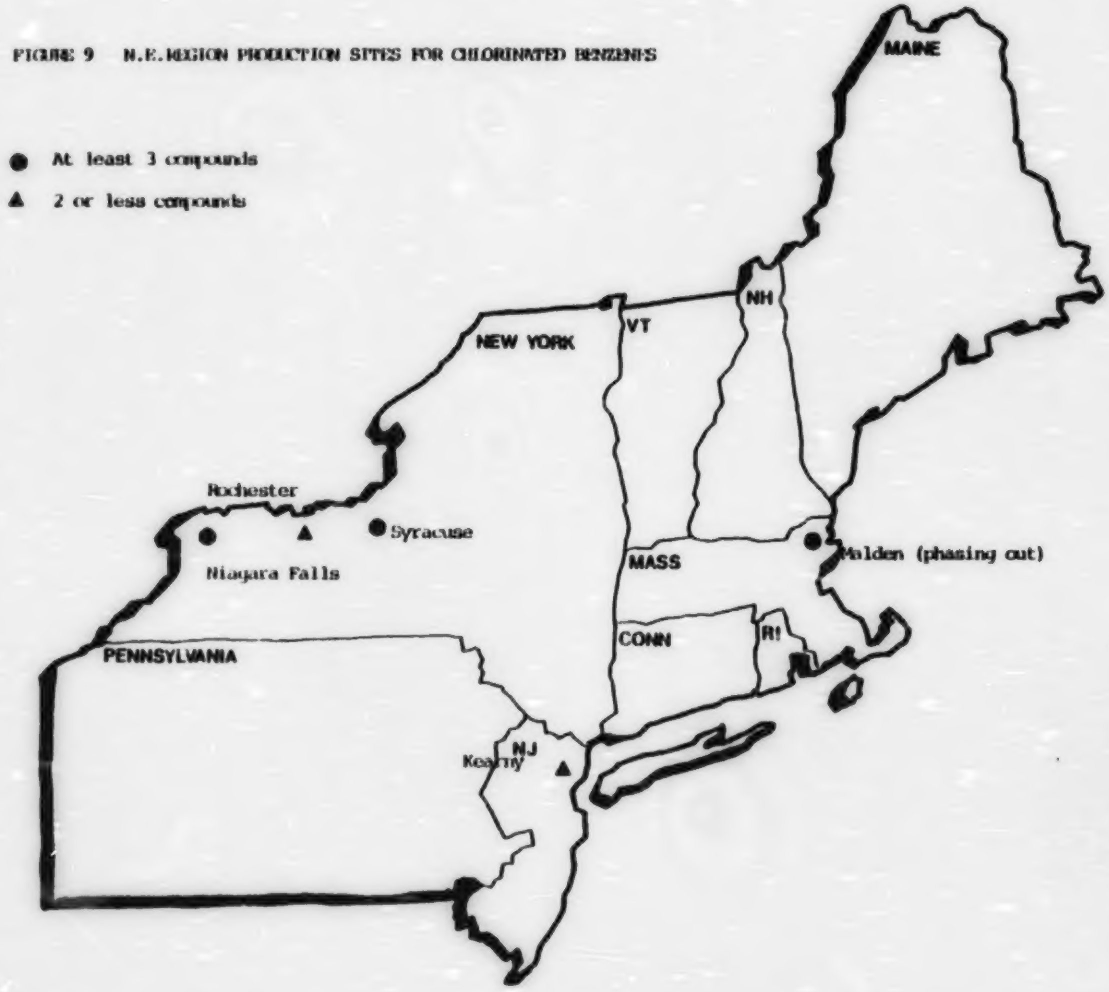

WASH
MONT
ORE
IDAHO
WY
CALIF
NEV
UTAH
COLO
ARIZ
N MEX
WEST
N DAK
S DAK
NEB
KAN
MINN
IOWA
MO
WIS
MICH
ILL
IND
OHIO
NORTH CENTRAL
NORTH EAST
ME
VT
NH
NY
MASS
RI
CONN
PA
NJ
MD
DEL
W VA
VA
KY
NC
TENN
SC
GA
ALA
MISS
ARK
LA
TEXAS
OKLA
FLA
SOUTH
● At least 3 compounds
▲ 2 or less compounds

FIGURE 9 N.E. REGION PRODUCTION SITES FOR CHLORINATED BENZENES


● At least 3 compounds
▲ 2 or less compounds
MAINE
NH
VT
NEW YORK
MASS
CONN
RI
NJ
PENNSYLVANIA
Rochester
Niagara Falls
Syracuse
Malden (phasing out)
Kearny

The most common catalyst used is sublimed ferric chloride (Hardie, 1964). Other catalysts employed include anhydrous aluminum chloride, stannic chloride, iron or aluminum. Addition of fuller's earth decreases production of dichlorobenzenes, while the aluminum chloride catalyst increases disubstitution (Hardie, 1964). The temperature of reaction is also a very important parameter. By manipulation of catalyst and reaction conditions, it is possible to maximize production of specific chlorobenzenes. However, it is not possible to avoid coproduction of higher substituted chlorobenzenes entirely.

Production of Monochlorobenzene

Prior to reaction, the benzene is dried by either azeotropic distillation or with silica gel, caustic soda or alumina (Hardie, 1964). Thiophene impurities do not affect the course of the reaction. Chlorine is scrubbed with concentrated sulfuric acid to dry and remove impurities. The reaction vessel is usually made from cast iron or mild steel. Cooling coils are made from steel and chlorine feed pipes are glass lined (Hooker Chemicals and Plastics Corp., 1977).

A continuous process, with immediate distillation of monochlorobenzene as it forms, decreases yield of dichlorobenzenes and may result in a product containing up to 95% MCB. The plant consists of a series of small externally cooled steel vessels containing the catalyst. Chlorine is piped into each vessel; at all times the chlorine concentration is kept to a minimum. At 20° to 40°C, monochlorobenzene forms and is removed from the excess benzene by fractional distillation. The benzene is recycled to the chlorinator. The by-product, hydrogen chloride, can be removed by washing with a refrigerated solvent. Holding the temperature below 40°C slows the rate of formation of chlorinated benzenes to one tenth that for monosubsititution (Hardie, 1964).

For batch production, the catalyst is usually ferric chloride. Again the temperature is kept below 45°C to minimize production of dichlorobenzenes (Hardie, 1964). Faith, Keyes and Clark (1965) described a higher temperature batch process for manufacture of chlorobenzene (see Figure 10). Chlorine is bubbled into a cast-iron or steel tank containing dry benzene with 1% its own weight of iron filings. Temperature is maintained at 40° to 60°C until density studies indicate that all the benzene is chlorinated. The temperature is raised to 55° to 60°C for six hours, when the density rises to 1.280 g/cm^3.

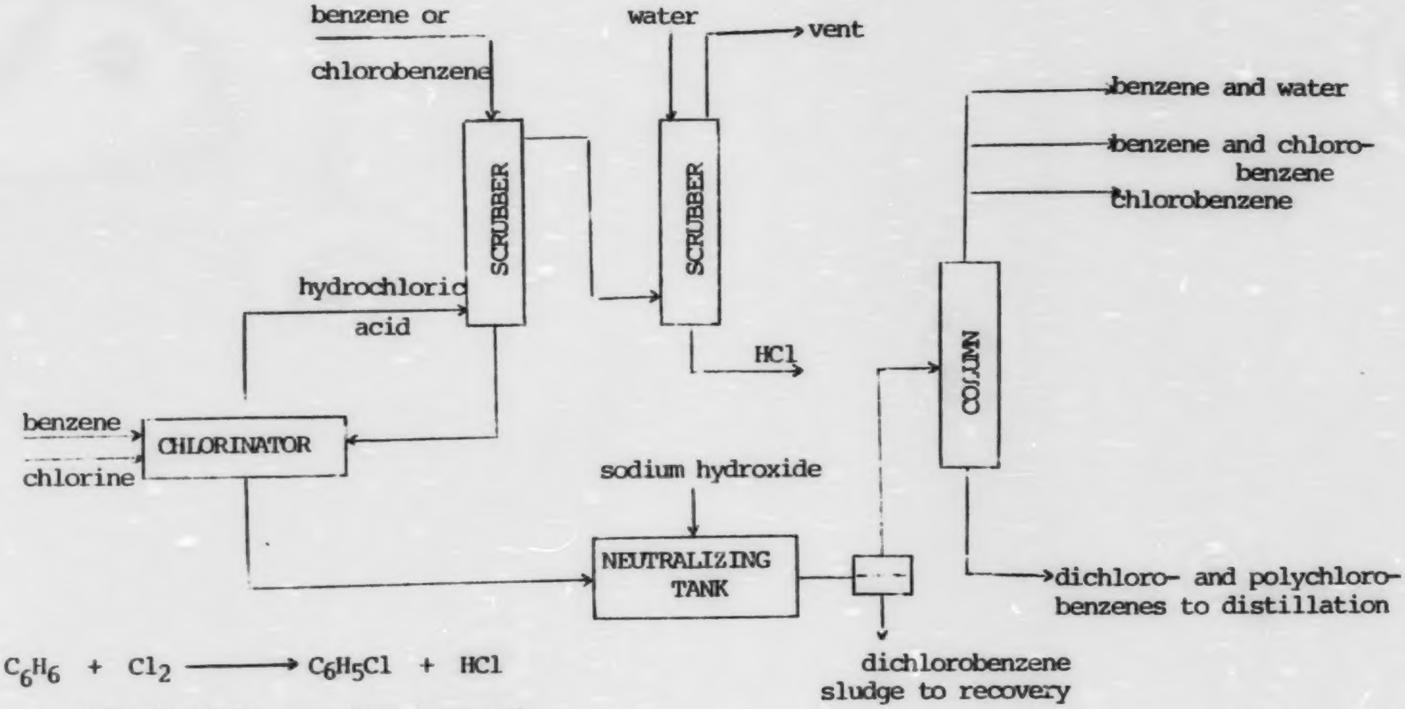
Chlorinated benzene is removed to an insulated steel tank with a reflux condenser. The mixture is agitated for several hours with a 10% caustic soda solution to remove HCl. Further agitation with 50% caustic soda at 60°C removes added chlorine. This neutralizing tank is heated by a steam jacket. The material then enters a separator where the alkaline sludge containing mainly dichlorobenzenes is removed for distillation. The lighter material is fractionally distilled to produce four fractions. Fractions one and two contain benzene, water, and chlorobenzene and are recycled for further processing. The third fraction contains chlorobenzene which is collected. The fourth fraction containing mainly dichloro- and trichlorobenzene is collected and fractionally distilled to separate the o- and p-dichlorobenzene isomers from 1,2,4-trichlorobenzene.

Hydrogen chloride formed in the chlorinator is led to a scrubber to remove benzene and chlorobenzene using a low vapor-pressure oil. The gas is then absorbed in water to give high quality hydrochloric acid.

At 100% chlorine consumption, the yield is approximately 80% MCB, 15% p-dichlorobenzene and 5% o-dichlorobenzene (Faith, Keyes and Clark, 1965).

FIGURE 10

PLANT DIAGRAM - CHLORINATION OF BENZENE
(Faith, Keyes and Clark, 1965)


benzene or
chlorobenzene
water
vent
SCRUBBER
SCRUBBER
hydrochloric
acid
HCl
benzene
chlorine
CHLORINATOR
sodium hydroxide
NEUTRALIZING
TANK
COLUMN
benzene and water
benzene and chloro-
benzene
chlorobenzene
dichloro- and polychloro-
benzenes to distillation
dichlorobenzene
sludge to recovery

$C_6H_6 + Cl_2 \longrightarrow C_6H_5Cl + HCl$

(70–75% yield, monochlorobenzene)

$C_6H_5Cl + Cl_2 \longrightarrow C_6H_4Cl_2 + HCl$

(10–20% yield, dichlorobenzene)

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Vapor phase chlorination of benzene takes place at 220° to 260°C in the Raschig process (Hardie, 1964). Hydrogen chloride is catalytically oxidized in a preheated mixture of benzene vapour, air and steam to form chlorine. The chlorine reacts with the benzene to form MCB. A mixed catalyst of copper oxide and transition metal oxides is contained on silica gel. Temperature control is accomplished by packing the catalyst in small diameter tubes. Only 10% of the benzene reacts at a time.

Dichlorobenzenes

Ortho- and para-dichlorobenzene can be produced by chlorinating benzene or chlorobenzene at 150° to 190°C with a ferric chloride catalyst (Hardie, 1964). The isomers may be separated by fractional distillation (b.p. ODCB - 179°C, b.p. PDCB - 173°C). Alternatively, PDCB can be crystallized out. Crystalline p-dichlorobenzene is washed with methanol and dried under vacuum at 100°C. PDCB can also be separated from the ortho isomer by treating the mixed isomers with chlorosulfonic acid at 15°C. p-Dichlorobenzene is separated from o-dichlorobenzene sulfonic acid by distillation.

An orienting catalyst such as benzene sulfonic acid or p-methyl benzene sulfonic acid will increase yields of p-dichlorobenzene to a high of 86% (Hardie, 1964).

1,2,4-Trichlorobenzene forms more rapidly by chlorination of o-dichlorobenzene than p-dichlorobenzene. Trichlorobenzene is easily separated from PDCB by fractional distillation (b.p. 210°C & 179.5°C, respectively). Thus, allowing the ODCB to form 1,2,4-trichlorobenzene is yet another way of isolating pure p-dichlorobenzene.

m-Dichlorobenzene may be prepared by isomerization of the o- and p-isomers by heating to 120°C under 650 psi pressure in the presence of a catalyst (Hardie, 1964). Catalysts used include aluminum chloride and hydrogen chloride. Alternatively, higher chlorinated benzenes can be catalytically reduced to m-dichlorobenzene. Trichlorobenzene mixtures have been reduced using molybdenum oxide, nickel chloride or chromium oxide as a catalyst. Hexachlorobenzene and hydrogen react at 350° to 500°C in the presence of a cuprous halide or alumina to form m-dichlorobenzene (Hardie, 1964).

Rucker (1960) described a method for selective hydrogenation of chlorobenzenes involving effective control of the degree of dehalohydrogenation by continuously fractionating the reaction products. The reaction takes place in the liquid phase from 100°C to the reflux temperature. Palladium (0.5% of 5% Pd) is deposited on activated charcoal as the catalyst. Hydrogen is led into the reaction vessel and as dehalogenation takes place, the products are continuously distilled off. As the lower chlorobenzenes are more volatile than the higher-substituted chlorobenzenes, any lighter product can be obtained from the starting material by controlling the distillation temperature. The chlorobenzenes are reduced at a rate almost directly proportional to their concentration in the reaction vessel.

According to Rucker, 100% m-dichlorobenzene can be formed by catalytically reducing 1,3,5-trichlorobenzene for 7 hours at 205°C. Excess hydrogen and by-product hydrogen chloride are removed through a reflux condenser.

Crowder and Gilbert (1958) patented a vapor-phase dehalogenation of 1,3,5-trichlorobenzene using platinum on activated charcoal as a catalyst at a temperature of 375°C and 1 psig pressure. Distillation of products was said to yield 65% m-dichlorobenzene. Other catalysts mentioned in the literature are cuprous chloride and titanium dioxide mixtures, nickel, nickel chromite, copper chromite, molybdenum oxide and chromium oxide.

Trichlorobenzenes

As indicated previously, 1,2,4-trichlorobenzene together with 1,2,3-trichlorobenzene are formed by catalytic chlorination of o-dichlorobenzene (Hardie, 1964). All three trichlorobenzenes may be obtained by reacting α -, β-, or γ-benzene hexachloride with alcoholic caustic potash. The 1,2,4-trichlorobenzene is formed by reacting α-benzene hexachloride with calcium hydroxide at 100°C (Hardie, 1964). All three isomers are produced when α-benzene hexachloride is dehydrohalogenated by pyridine. Further manufacturing details are not available.

Tetrachlorobenzenes

Tetrachlorobenzenes may be prepared from trichlorobenzenes as indicated below. Kissling (1957) patented a method to separate pure 1,2,4,5-tetrachlorobenzene from a mixture of trichloro-, pentachloro- and other tetrachlorobenzene isomers by fractional crystallization in acid solution. Hydrogen chloride concentration should be 0.2 moles HCl/mole tetrachlorobenzene and the concentration of a Friedel-Crafts catalyst should be from 0.01 to 5% by weight. Optimum temperatures for crystallization are in the range 0° to 30°C.

Routes to Tetrachlorobenzenes (Hardie, 1964)

$$\text{1,2,3-trichlorobenzene} \xrightarrow[\text{catalyst}]{Cl_2} \text{1,2,3,4-tetrachlorobenzene}$$

$$\text{1,3,5-trichlorobenzene} \xrightarrow[\text{aluminum amalgam}]{Cl_2} \text{1,2,3,5-tetrachlorobenzene}$$

$$\text{1,2,4-trichlorobenzene} \xrightarrow[\text{aluminum amalgam}]{Cl_2} \text{1,2,4,5-tetrachlorobenzene}$$

$$\text{1,2,4-trichlorobenzene} \xrightarrow[\text{(nitration, reduction, diazotization)}]{\text{Sandmeyer reaction}} \text{1,2,4,5-tetrachlorobenzene}$$

2,3,5-trichloroaniline $\xrightarrow[\text{Sandmeyer reaction}]{}$ 1,2,3,5-tetrachlorobenzene

Note: Yields not indicated

The hydrogen chloride produced as a by-product of the chlorination of benzene or chlorobenzenes remains in the reaction vessel to facilitate the crystallization. Crystals of 1,2,4,5-tetrachlorobenzene are filtered, centrifuged or decanted, and washed with either methanol, ethanol, acetone and/or liquid chlorobenzenes. The supernatant liquid still contains up to 50% of the 1,2,4,5-tetrachlorobenzene formed. Further cooling will precipitate a second crop of 1,2,4,5-tetrachlorobenzene.

Pentachlorobenzene

Pentachlorobenzene may be formed by chlorination of benzene in the presence of ferric chloride at 150° to 200°C, or by chlorination of any of the lower chlorobenzenes (Mumma and Lawless, 1975). A production schematic for pentachlorobenzene (or quintochlorobenzene, QCB) is shown in Figure 11. Chlorination of 1,3,4,5-tetrachlorobenzene is faster than chlorination of 1,2,4,5-tetrachlorobenzene (Hardie, 1964).

(b) FLUORINATED BENZENES

1. Quantity Produced, Market Trends

Little numerical data exists to document the quantities of fluorobenzenes produced or processed in this country. Limited imports of monofluorobenzene and hexafluorobenzene are reported by USITC (1971b-74b)(see Table 19).

No conclusions regarding market trends can be gathered from such scanty information. Some new uses of the compounds which would expand the market are still under evaluation (see Section IIB below).

FIGURE 11 PRODUCTION SCHEMATIC FOR PENTACHLOROBENZENE BY CHLORINATION OF BENZENE, CHLOROBENZENE (Mumma and Lawless, 1975)

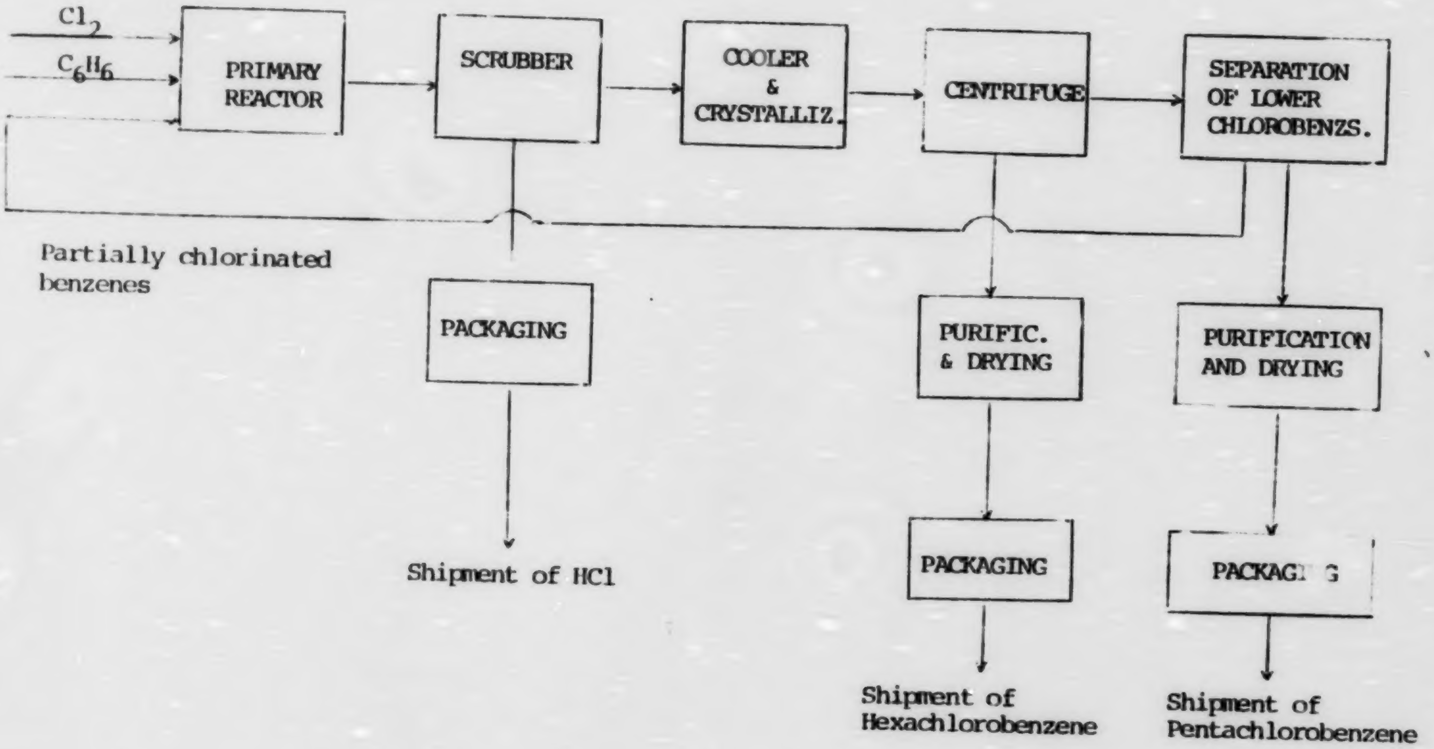

Cl_2
C_6H_6
PRIMARY REACTOR
SCRUBBER
COOLER & CRYSTALLIZ.
CENTRIFUGE
SEPARATION OF LOWER CHLOROBENZS.
Partially chlorinated benzenes
PACKAGING
PURIFIC. & DRYING
PURIFICATION AND DRYING
PACKAGING
PACKAGING
Shipment of HCl
Shipment of Hexachlorobenzene
Shipment of Pentachlorobenzene

TABLE 19

IMPORTS OF FLUORINATED BENZENES (in pounds)
(USITC, 1971b-74b)

	1971	1972	1973	1974
Monofluorobenzene	11,059	42,037	58,071	29,089
Hexafluorobenzene	55	220	35	-
p-Bromofluorobenzene	-	-	-	222

2. Producers, Processors and Production Sites

According to the Stanford Research Institute (1976), fluorobenzenes are manufactured by the Olin Corporation, the Aldrich Chemical Company, PCR Industries and Whittaker Chemicals. The Olin Handbook of Aromatic Fluorine Compounds (Olin Chemicals, 1974) lists 145 fluorobenzenes containing only fluorine or fluorine with chlorine, bromine and/or iodine to form mixed halogenated benzenes. The Olin Corporation (1976) reported that the company does not manufacture any simple fluorobenzenes as defined in this report. The firm purchases monofluorobenzene to manufacture fluorinated benzenes with additional non-halogen groupings in the molecule.

The Whittaker Corporation is listed both by Stanford Research Institute (1975a, 1976) and USITC (1975a) as producing hexafluorobenzene. On contact, Whittaker indicated that the Corporation does not now, nor has ever, manufactured this or any other halogenated benzene compound (Whittaker, 1976). The company operated a high technology research and development activity in the San Diego area under contract with the U.S. Government. It was suggested that the above reports of hexafluorobenzene manufacture "perhaps" refer to this work related to the space and missile fields.

TABLE 20 U.S. MANUFACTURE OF FLUORINATED BENZENES

	Olin Chem.	Aldrich Ch.	PCR Indust.	Whittaker
Fluorobenzene	o	o		
o-Difluorobenzene	o			
m-Difluorobenzene	o			
p-Difluorobenzene	o			
Hexafluorobenzene			o[1]	o ▲[2]

▲ USITC 1975a

o Stanford Research Institute, 1975a

1 Processor not manufacturer (PCR Industries, 1976b)

2 Does not manufacture hexafluorobenzene though "may have done so" for U.S. Government contracts in the space and missile field (Whittaker, 1976).

	Olin Chem.	Aldrich Ch.
o-Bromofluorobenzene	o	
m-Bromofluorobenzene	o	
p-Bromofluorobenzene	o	o
o-Chlorofluorobenzene	o	
2,4-Dibromofluorobenzene	o	
m-Chlorofluorobenzene	o	
p-Chlorofluorobenzene	o	

Locations

The Olin Corporation is located at Rochester, New York and the Aldrich Chemical Company is operational at Milwaukee, Wisconsin.

Note: The Olin Corporation indicates that it does not currently manufacture any simple fluorinated benzenes, but purchases monofluorobenzene for use as an aromatic intermediate.

PCR Industries does not manufacture hexafluorobenzene either (PCR Industries, 1976b) though the firm offers several fluorobenzenes for sale including monofluorobenzene, hexafluorobenzene, iodopentafluorobenzene, 1,2,3,5-tetrafluorobenzene, 1,2,4,5-tetrafluorobenzene, 1,2,4- and 1,3,5-trifluorobenzene and *o*-, *m*- and *p*-difluorobenzene (PCR Industries, 1976a). PCR Industries (1976b) indicated that fluorobenzenes are imported from England and Germany.

The Aldrich Chemical Company offers a variety of fluorobenzenes through Aldrich Chemicals and through the Alfred Bader Chemical Division.

TABLE 21

FLUORINATED BENZENES AVAILABLE THROUGH ALDRICH CHEMICALS
(Aldrich Chemical Co., 1976)

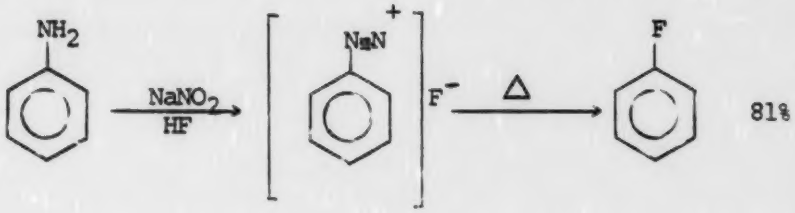
Available through Aldrich Chemicals	Available through Alfred Bader Chemicals
o-Difluorobenzene	1,2-Dichloro-4-fluorobenzene
2,4-Dibromo-1-fluorobenzene	*1,2-Diiodotetrafluorobenzene
1-Chloro-3-fluorobenzene (99%)	*1,4-Dibromotetrafluorobenzene
1-Chloro-2-fluorobenzene (99%)	1,2-Dibromotetrafluorobenzene
2-Bromofluorobenzene (99%)	*1,3-Dibromotetrafluorobenzene
3-Bromofluorobenzene (99%)	2-Fluoroiodobenzene
4-Bromofluorobenzene (97%)	1,3-Dichloro-4-fluorobenzene
Bromopentafluorobenzene	3-Chloroiodobenzene
Monofluorobenzene (99%)	4-Fluoroiodobenzene
m-Difluorobenzene (97%)	
p-Difluorobenzene (98%)	
Hexafluorobenzene (99%)	
Pentafluorobenzene (98%)	
1,2,3,4-Tetrafluorobenzene (98%)	
1,2,3,5-Tetrafluorobenzene (99%)	
1,2,4,5-Tetrafluorobenzene (98%)	

* Retail at $10/5g

The Alfred Bader Chemical Division sells chemicals gathered from laboratories in universities and other institutions in this country and throughout the world. It was not possible to pinpoint the sources of this very diverse and specialized collection. Aldrich Chemicals manufactures some of these fluorinated benzenes, while purchasing others from different companies. More complete information was not available.

3. Production Methods and Processes

Monofluorobenzene cannot be prepared by direct fluorination of benzene, but is generally manufactured through the Sandmeyer reaction. According to Barbour et al. (1966), in Germany quantities of as high as 1000 kg have been batch-prepared at yields of 81%. Aniline is diazotized in anhydrous hydrogen fluoride.



Barbour et al. did not mention a catalyst, but presumably the thermal decomposition of the diazonium compound can be controlled by use of a cuprous salt. Lower yields of monofluorobenzene result from the reaction of a solution of benzene diazonium chloride with fluoroboric acid at 10°C (50 to 60%) (Fieser and Fieser, 1960). Fluoroboric acid is made by dissolving solid boric acid in 60% hydrofluoric acid. Barbour et al. (1966) gave the following yields for preparation of small quantities of monofluorobenzene:

benzene diazonium fluoroborate	51%
benzene diazonium fluorosilicate	30%
benzene diazonium hexafluorophosphate	60-75%

Engineering details were not available for preparation of fluorobenzenes, in fact many of these compounds are only prepared in small quantities on the bench scale. The o-, m- and p-difluorobenzenes are usually prepared through Balz-Schiemann procedures (Barbour et al., 1966). The meta isomer is prepared through diazotization of m-phenylenediamine. The diazonium salt (usually the chloride) is treated with 45% fluoroboric acid at 0°C to form bisdiazonium fluoroborate. Decomposition of the bisdiazonium salt gives a 73% yield of 1,3-difluorobenzene.

p-Difluorobenzene is similarly prepared from p-phenylenediamine. Yields are lower (60%), but may be improved by decomposing 1,4-bisdiazonium fluoroborate in aqueous acetone with cuprous chloride. Separation of difluorobenzene from the reaction mixture may be accomplished by steam distillation.

o-Difluorobenzene is prepared from o-nitroaniline by first substituting one fluorine through the Balz-Schiemann reaction described above. The nitro group is reduced and the second fluorine atom is introduced into the molecule through a second Balz-Schiemann reaction.

Diazotization of 2,5-difluoroaniline (Balz-Schiemann) yields only 30% of 1,2,4-trifluorobenzene (Barbour et al., 1966). Yields of this isomer are higher by boiling 2,3,5,6-tetrafluorophenylhydrazene with 3N caustic soda (up to 61%).

The 1,3,5-trifluoro compound can also be prepared through a Balz-Schiemann diazotization of 3,5-difluoroaniline. Yields of 60% have been reported.

N-methyl pyrrolidone, tetramethylene sulfone (sulfolane) and dimethyl formamide have all been successfully used as solvents.

Yields are higher and the product mixture less complicated using sulfolane as the solvent. At temperatures below 200° and reaction times less than 12 hours, the reaction is cleaner and yields are higher. However, the degree of fluorination is less (Holbrook *et al.*, 1966). Although hexabromobenzene can be produced in a polar solvent, hexachlorobenzene can be hexafluoro substituted using potassium fluoride without a solvent. The reaction takes place under pressure at 400° to 500°C. Again, a mixture of chlorofluorobenzenes is formed (Barbour *et al.*, 1966), e.g.:

$$C_6Cl_6 \xrightarrow{KF} \underset{21\%}{C_6F_6} + C_6Cl_2F_4 + C_6Cl_3F_3$$

Commercially, 1,2,3,4-tetrafluorobenzene is prepared by fluorinating benzene with cobalt trifluoride. The polyfluorinated cyclohexenes formed are dehydrofluorinated to mixed products including 1,2,3,4-tetrafluorobenzene. The 1,2,3,5- and the 1,2,4,5-tetrafluorobenzene may be similarly prepared through the fluorocyclohexene. The fluorination of hexachlorobenzene with potassium fluoride (see above) gives varying yields of 1,2-dichlorotetrafluorobenzene which is dechlorinated to form 1,2,3,5-tetrafluorobenzene. 1,2,4,5-tetrafluorobenzene is produced in 90% yield through heating pentafluorophenylhydrazine with caustic soda (*2N*) (Barbour *et al.*, 1966).

Pentafluorobenzene may also be prepared starting from benzene and fluorinating with cobalt trifluoride to produce isomers of octafluorocyclohexane which are dehydrofluorinated with concentrated potassium hydroxide. Defluorination of 1,3- and 1,4-heptafluorocyclohexadienes also produces pentafluorobenzene. The dienes are formed by dehydrofluorination of nonafluorocyclohexanes (Barbour et al., 1966).

Hexafluorobenzene is also prepared commercially through the diene route starting with benzene and cobalt trifluoride. The initial reaction takes place at 150°C. Treatment with aqueous sodium or potassium hydroxide converts the mixture of fluorocyclohexanes to polyfluorocyclohexenes and hexadienes. Passage of these cyclic aliphatic fluorocarbons in the vapor phase over a heated metal (iron or nickel gauze) results in defluorination (Coe et al., 1960). The reaction takes place in a nitrogen atmosphere. Hexafluorobenzene (9%) can be separated from the coproducts, pentafluoro- and tetrafluorobenzene, by fractional distillation.

Falk (1963) described the pyrolysis of dichlorofluoromethane as a route to hexafluorobenzene, chloropentafluorobenzene, and dichlorotetrafluorobenzene. At 650° to 720°C, dichlorofluoromethane decomposes on passage through a nickel tube to furnish 4 to 4.5% (by wt.) hexafluorobenzene. The compound is separated from other products by fractional distillation and purified by freeze-filtering the distillate. The filtrate is evacuated at low temperatures to give hexafluorobenzene of 99% purity.

Chloropentafluorobenzene is separated from the product mixture by fractional distillation (b.p. range 108° to 124°C). Freeze filtering produces a compound of 65% purity. Dichlorotetrafluorobenzene distills as a higher boiling fraction between 156° to 162°C. Both compounds are purified by column chromatography. Yields of chloropentafluorobenzene are less than 5%, and yields of dichlorotetrafluorobenzene are below 2%.

Copyrolysis of dichlorofluoromethane ($CHCl_2F$) and chlorofluoromethane

(CH_2ClF)) at 650° to 730°C is reported to give 6 to 10% pentafluorobenzene, 5 to 8% hexafluorobenzene, 5 to 8% chloropentafluorobenzene, and 2 to 4% dichlorotetrafluorobenzene (Falk, 1963).

4. Market Prices

The catalogue prices for fluorinated benzenes are as follows (see Tables 21 and 22): (a) All Alfred Bader Division chemicals listed retail for $10/5g unless indicated by an asterisk*; all items marked * are available at $10/250 mg; (b) all PCR Chemicals have the following market prices (list correct as of March 1, 1976) in dollars:

TABLE 22

MARKET PRICES OF FLUORINATED BENZENES($'s)
(PCR Industries, 1976a)

	1g	5g	10g	25g	50g	100g	250g	1k
Monofluorobenzene	-	-	-	-	-	-	15.25	53.50
o-Difluorobenzene	-	-	-	28.50	-	100	-	-
m-Difluorobenzene	-	-	-	39	-	136	-	-
p-Difluorobenzene	-	-	-	18	-	63	-	-
1,2,3-Trifluorobenzene	-	-	-	-	-	-	-	-
1,2,4-Trifluorobenzene	9.90	40.00	-	-	-	-	-	-
1,3,5-Trifluorobenzene	-	16.10	-	57	-	-	-	-
1,2,3,4-Tetrafluorobenzene	-	-	-	-	-	-	-	-
1,2,3,5-Tetrafluorobenzene	-	25	-	-	-	-	-	-
1,2,4,5-Tetrafluorobenzene	-	25	-	-	-	-	-	-
Pentafluorobenzene	-	-	12	-	40	-	-	-
Hexafluorobenzene	-	-	-	30	-	90	-	-
Iodopentafluorobenzene	-	12	-	36	-	-	-	-

As is clear from the above table, the fluorinated benzenes are expensive chemicals sold only in small quantities.

(c) BROMINATED BENZENES

1. Quantity Produced, Market Trends

It was not possible to document the quantities of bromobenzene produced or processed in this country. USITC reports did not contain any reference to imports of brominated benzene compounds, except for a listing of *p*-bromofluorobenzene (222 pounds) imported in 1974 and imports of hexabromobenzene in 1972 (7,165 pounds) and 1973 (9,909 pounds). Manufacturers considered such data to be confidential and were unable to give estimates. While it appears that brominated compounds could be used instead of the corresponding chlorinated compounds where properties are equivalent, the higher costs of the brominated compounds make this substitution unlikely. Also, there does not appear to be any substitution likely on the grounds of improved ecotoxicological properties (*vide infra*).

2. Producers, Processors and Production Sites

USITC (1974a) listed Dow Chemical, Midland, Michigan, as a manufacturer of monobromobenzene, *p*-dibromobenzene, and *p*-bromochlorobenzene. Stanford Research Institute (1976) also listed Dow Chemical for the three bromobenzenes and additionally cited the Northrop Carolina Company as a producer of tribromobenzene (isomer not specified). Dow Chemical reported that it no longer manufactures any brominated benzenes though retaining the capacity to do so (Dow Chemical, 1977a). Three companies listed as manufacturers of hexabromobenzene have all ceased production in the last few years (see Table 23). They indicated that the Cyanamid Company was the principal purchaser of hexabromobenzene, and that without its business, they were unable to manufacture the compound profitably. Great Lakes Chemical Corp. (1976) stated that Cyanamid no longer purchased hexabromobenzene, but had replaced the fire-retardant material with decabromodiphenyloxide.

A number of brominated compounds as well as mixed halogens are available through the Aldrich Chemical Company. It is not clear if Aldrich Chemical produces or processes these chemicals. The following chemicals are available through the Alfred Bader Chemical Division: 1-bromo-2,5-dichlorobenzene; 1-bromo-2,4-dichlorobenzene; 1-iodo-2,4,6-tribromobenzene. Aldrich Chemicals sells bromobenzene, o- and p-dibromobenzene, 1,3,5-tribromo-, hexabromobenzene and the following mixed halogenated benzenes: 2-bromochloro- and 4-bromochlorobenzene.

3. Production Methods and Processes

Heating molar equivalents of bromine and benzene in the presence of a bromine carrier (usually iron filings) results in formation of monobromobenzene. Varying amounts of o- and p-dibromobenzene are coproduced with the monocompound. Dibromination results in production of approximately 70% p-dichlorobenzene and 30% o-dichlorobenzene. Further bromination results in formation of 1,2,4-tribromobenzene and 1,2,4,5-tetrabromobenzene (cf. chlorobenzene). Hydrogen bromide is formed as a by-product of each bromo-substitution reaction.

$$C_6H_6 + Br_2 \longrightarrow C_6H_5Br + HBr, \quad 2\ C_6H_5Br_2 + Br_2 \longrightarrow 2\ C_6H_4Br_2 + 2\ HBr$$

The products are separated by fractional distillation. Preparation of the highly brominated benzenes can be readily accomplished by reaction of benzene with dibromoisocyanuric acid in concentrated sulfuric acid, oleum or

TABLE 23

U.S. MANUFACTURERS OF BROMINATED BENZENES

	Dow Chem.	Michigan Chem. Corp.	Nease Chem.	Northrop Carolina Co.	White Chem. Corp.	Great Lakes Chem. Corp.
Bromobenzene	▲ ○[1]					▲
p-Dibromobenzene	▲ ○[1]					
Tribromobenzene[2]	▲ ○[1]			○		
Hexabromobenzene		▲ ○[1]	▲		○[1]	○[1]
p-Bromochlorobenzene	▲ ○[1]					

Key

▲ USITC 1975a

○ Stanford Research Institute, 1976

* Personal Communication

1 no longer produces this compound

2 isomer not specified

Note

The White Chemical Corporation, Great Lakes Chemical Corporation and the Michigan Chemical Corp. have all ceased production of hexabromobenzene within the past few years. The chemical was purchased largely by Cyanamid as a fire-retardant for monacrylic carpet fibers (Great Lakes Chemical Corp., 1976). As hexabromobenzene sublimes, it is hardly the ideal fire-retardant, and has been replaced by decabromodiphenyloxide.

fluorosulfonic acid (Feast and Musgrave, 1971).

As in the preparation of chlorobenzenes, the use of a different catalyst alters the yield of products. p-Dibromobenzene can be manufactured from benzene in yields as high as 85% with ferric bromide as the carrier (Fieser and Fieser, 1967). Yields of 61 to 71% are reported for aluminum bromide as catalyst (Fieser and Fieser, 1960). The temperature of reaction is usually around 40°C. At elevated temperatures, meta substitution increases, so that at 500°C, bromination of monobromobenzene results in 57% yield of m-dibromobenzene (Sykes, 1963).

Shell Chemicals reported that bromination between 75°C and 120°C in the presence of an aluminum halide increases yield of m-dibromobenzene. The firm indicated that for good yields of the meta compound, the catalyst should be present in low amounts (2 to 6% of total) and gradually added to the reaction mixture as the bromination proceeds. This technique results in yields of the meta isomer exceeding 50% starting from either benzene or monobromobenzene, and with either aluminum chloride or bromide as the carrier. It is difficult to separate the m- and o-dibromobenzenes by fractional distillation because of the closeness of their boiling points (220°C and 225°C, respectively).

Hexabromobenzene is manufactured by treating hexachlorobenzene with excess bromine trifluoride. The mixture is heated with antimony pentafluoride, and the intermediates washed and refluxed in alcohol with zinc dust. Engineering details were not available for this and the other processes described above.

4. Market Prices

Great Lakes Chemical Corp. (1975) provided the following market prices for monobromobenzene (F.O.B. El Dorado, Arkansas):

Standard Truckload 39,000 lbs (65 drums)	$0.92/lb
24,000 - 38,400 lbs (40-64 drums)	0.93/lb
2,400 - 23,400 lbs (4-39 drums)	0.95/lb
600 - 1,800 lbs (1- 3 drums)	0.99/lb

As can be seen above, monobromobenzene is appreciably more expensive than monochlorobenzene (q.v.). Catalogue price of hexabromobenzene as quoted by PCR Industries (1976a) is $5 for 5g.

(d) IODINATED BENZENES

1. Production and Market Trends

USITC reports from 1971 to 1974 contain no reference to imports of any of the iodinated benzenes. Very little information was found relating to production of iodobenzene, thus it is not possible to make any comment on future markets.

2. Producers, Processors, and Production Sites

Eastman Kodak Organic Chemicals Division is a manufacturer of iodobenzene (Eastman Kodak, 1976) and according to USITC (1974a) and Stanford Research Institute (1974, 1975a, 1976) they have also produced m-iodobenzene (see Table 24). The company also manufactures small quantities of p-iodobenzenesulfonyl chloride for laboratory use. No additional information was found relating to major production of iodobenzene.

3. Prodution Methods and Processes

Iodobenzene cannot be prepared by direct iodination of benzene unless an oxidizing agent such as concentrated nitric acid is present. Then the reaction yield is 86 to 87% with traces of nitrobenzene contaminating the product (Fieser and Fieser, 1960). Alternatively, iodobenzene can be prepared in yields in excess of 80% through diazotization of aniline followed by reaction with potassium iodide (Feast and Musgrave, 1971). The compound can also be synthesized by addition of iodine to benzene with peracetic acid as the oxidizing agent (Fieser and Fieser, 1967).

o-Bromoiodobenzene is prepared from o-bromoaniline through the Sandmeyer reaction as described previously. Note: Mixed halogenobenzenes are most easily obtained through the diazonium compound prepared from the corresponding halogen-substituted aniline. Also, halogen exchange is possible in polar solvents such as sulfolane (q.v. fluorobenzenes) through reaction with the sodium or potassium halide. Fluorine cannot be replaced by this method.

Polyiodobenzenes are formed when iodine reacts with benzene in the presence of sulfuric acid. Control of temperature and concentration of acid varies the degree of iodination. Hexaiodobenzene has been prepared in 80% yield using 60% oleum at 170° to 180°C (Feast and Musgrave, 1971).

TABLE 24

U.S. MANUFACTURE OF IODINATED BENZENES

	Eastman Kodak	RSA Chemical
Monoiodobenzene	*	1 ○
m-Diiodobenzene	▲ ○	
p-Diiodobenzene		1 ○

▲	USITC, 1975a
○	Stanford Research Institute, 1975a
*	Personal Communication, Eastman Kodak, 1976
1	RSA has not manufactured iodobenzenes for five years - they will manufacture to order (RSA Chemicals, 1976). The firm states that principal imports of iodobenzenes come from W.Germany and Scandinavia.

B. USES

(a) CHLORINATED BENZENES

1. Major and Minor Uses

Monochlorobenzene

The bulk of monochlorobenzene manufactured in the mid 1960's was used to produce phenol (60%), DDT (25%) and aniline (Hardie, 1964). The 1973 consumption pattern is shown in Table 25.

TABLE 25

1973 CONSUMPTION OF MONOCHLOROBENZENE
(Lewis, 1975)

Chemical	Consumption
Phenol	123 million pounds
o- and *p*-Nitrochlorobenzene	140
Solvent uses	75
DDT	30
Other	30
Total	398

The market for monochlorobenzene is in considerable flux, so it is possible that the 1973 consumption pattern given is now out-of-date. The decrease in DDT production from 1964 to 1973 is indicative of regulatory action limiting usage of DDT in this country, and world poverty restricting purchases of DDT for the World Health Organization malaria control program (Chemical Marketing. Reporter, 1974a).

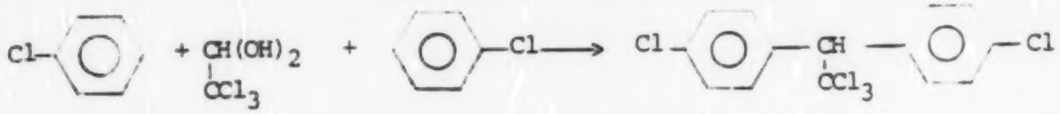
Hydrolysis of monochlorobenzene by dilute caustic soda at 300°C and 2000 to 3,000 psig pressure forms sodium phenylate which reacts with hydrochloric acid to yield phenol (Fieser and Fieser, 1960). In a continuous modification of this process, the reactants pass along a mile long tube for twenty minutes

$$C_6H_5Cl \xrightarrow[2000 - 3000\ \text{psig}]{300°\text{C}\quad \text{NaOH}} C_6H_5ONa \xrightarrow[\text{HCl}]{} C_6H_5OH$$

Diphenyl oxide is formed in a side reaction of the phenylate and the phenol. As this reaction is reversible, accumulation of the oxide is minimized by recycling the equilibrium mixture. Tarry wastes remaining after distillation of the phenol contain 20 to 25% o- and p-hydroxydiphenyl. The diphenyl ethers are formed through condensation of chlorobenzene with phenol, and by condensation of two molecules of chlorobenzene to chlorodiphenyls which hydrolyze to the hydroxydiphenyl compounds. In the U.S., this reaction is now used only by Dow Chemical, the firm which initially developed the process in 1928. Dow Chemical is phasing out manufacture of phenol from chlorobenzene, preferring the more convenient route from cumene (Chemical Marketing Reporter, 1975).

Phenol can also be prepared from chlorobenzene by the Raschig process. As described previously, hydrogen chloride is catalytically oxidized at 230°C to form chlorine which chlorinates the benzene. At 425°C and with a catalyst, the chlorobenzene hydrolyzes to phenol (Fieser and Fieser, 1960).

DDT is prepared by condensation of chlorobenzene with chloral hydrate in the presence of sulfuric acid (Fieser and Fieser, 1960).



DDT (dichlorodiphenyltrichloroethane)

Other isomers of DDT are also formed, with the p,p' compound the most biologically active. Production has dropped from nearly 180 million pounds in 1963 to 59 million pounds in 1970 (Lewis, 1975). The DDT contains MCB as an impurity (Lewis, 1975).

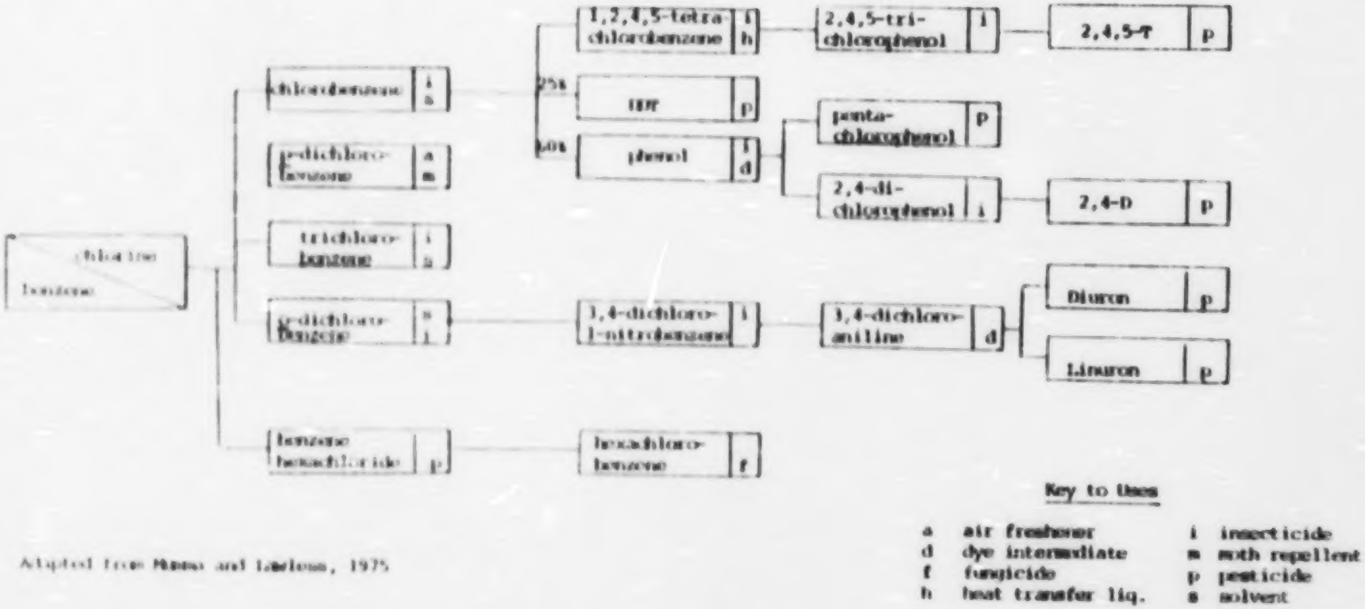
High yields of *o*- and *p*-chloronitrobenzene are produced from MCB by E.I. duPont de Nemours and Co., Inc. at Deepwater, New Jersey, and by Monsanto Industrial Chemicals Co. at Sauget, Illinois. These chloronitrobenzenes are converted to intermediates such as *p*-nitroaniline and *p*-nitrophenol. The phenol is mainly used to manufacture the pesticides, parathion and methyl parathion (Lewis, 1975). Phenylenediamine, an important dye intermediate, is produced from *o*-chloronitrobenzene by American Color and Chemical Corp. (Lockhaven, Pennsylvania) and by E.I. duPont de Nemours and Co., Inc., at Deepwater, New Jersey. The latter firm indicated a moderate growth in use of chloronitrobenzene (Lewis, 1975).

Monochlorobenzene reacts with ammonia at 340°C and 340 atmospheres to form aniline though MCB is rarely used as a precursor to aniline. Aniline is an important intermediate in the dye industry and is more commonly manufactured by reduction of nitrobenzene.

As indicated in Figure 12, a quantity of chlorobenzene can be further chlorinated to form 1,2,4,5-tetrachlorobenzene. The 1973 estimated production of 1,2,4,5-tetrachlorobenzene was 18 million pounds (Lewis, 1975).

Allied Chemical Corporation (1973) cited usage of monochlorobenzene as a solvent in the manufacture of adhesives, paints, polishes and waxes. The firm also cited use of monochlorobenzene as an inert process solvent for the manufacture of diisocyanates, pharmaceuticals and natural rubber, and as a dye carrier in textile dying. Chlorobenzene is a valuable solvent, partly because of its non-corrosive nature and its ability to dissolve many compounds. The Mobay Chemical Company (New Martinsville, West Virginia, and Cedar Bayou, Texas) and the Upjohn Company (La Porte, Texas) are two producers of isocyanates who use MCB as a solvent (Lewis, 1975).

FIGURE 12 CONSUMPTION PATTERN FOR CHLORINATED BENZENES


chlorine
benzene
chlorobenzene i s
p-dichlorobenzene a m
trichlorobenzene i s
o-dichlorobenzene s i
benzene hexachloride p
25%
60%
1,2,4,5-tetrachlorobenzene i h
DDT p
phenol i d
3,4-dichloro-1-nitrobenzene i
hexachlorobenzene f
2,4,5-trichlorophenol i
pentachlorophenol p
2,4-dichlorophenol i
3,4-dichloroaniline d
2,4,5-T p
2,4-D p
Diuron p
Linuron p
Key to Uses
a air freshener
d dye intermediate
f fungicide
h heat transfer liq.
i insecticide
m moth repellent
p pesticide
s solvent

Adapted from Mumma and Lawless, 1975

o-Dichlorobenzene

Lewis (1075) estimated the following distribution for o-dichlorobenzene: 61% to organic synthesis; 20% to toluene diisocyanate production; 12% miscellaneous solvents; and 7% to other uses.

Brown et al. (1975) indicated that approximately 29% of annual production of o-dichlorobenzene is used as an inert process solvent for toluene diisocyanate (TDI) production. This figure represents 50% of the quantity of ODCB manufactured annually which goes to nonintermediate dispersive use. Lewis (1975) stated that ODCB use is expected to grow at a 9% annual rate through 1977, with solvent use for TDI production representing the bulk of the growth. In synthesis of TDI, phosgene is treated with toluene diamine in ODCB solution. MCB is also used as a solvent for TDI manufacture.

MANUFACTURERS OF TOLUENE DIISOCYANATE
(Lewis, 1975)

Company	Location	1973 Capacity (millions of pounds)
Allied Chemical Corp.	Moundsville, W.Va.	70
BASF Wyandotte Corp.	Geisman, La.	40
E.I. duPont de Nemours and Co., Inc.	Deepwater, N.J.	170
Mobay Chemical Co.	New Martinsville, W. Va.	200
Mobay Chemical Co.	Cedar Bayou, Tex.	150
Olin Corp.	Ashtabula, Oh.	40
Olin Corp.	Lake Charles, La.	90
Rubicon Chemicals, Inc.	Geisman, La.	110
Union Carbide Corp.	Institute, W. Va.	55
	Total	925

ODCB is non-corrosive and stable, and so finds use as a solvent for soft carbon deposits, and tars and wool oils in the textile industry (Dow Chemical, 1975b). Allied Chemical Corporation (1973) indicated that ODCB is used to degrease leather and metals, and together with emulsified muriatic acid is found as a grease solvent in formulated toilet bowl cleaners. Solvent uses of ODCB account for some 20% of production (i.e. approximately 42% of dispersive use - Brown et al., 1975). ODCB is also used to remove lead, gum and resins from automobile and aircraft engine parts (Allied Chemical Corp., 1973; Hardie, 1964). Lewis (1975) reported that because of environmental concern, use of ODCB as an aircraft engine degreaser has slumped. Barsol®, cresylic solvents and aqueous alkalis are being substituted for ODCB. Though only small amounts of ODCB are used to clean automobile engines, the use is fairly widely spread (Lewis, 1975).

According to Allied Chemical Corp. (1973), ODCB is used to strip neoprene tank linings, and will form a rustproofing mixture with high boiling alcohols. The use of ODCB as an odorant is reportedly limited (Midwest Research Institute, 1974) but appears to be increasing, as ODCB has been found in industrial wastewater effluents throughout the country (Kopp, 1977).

ODCB is a very important intermediate for manufacture of the herbicides, diuron and linuron. Dupont manufactures diuron, monuron and neburon at La Porte, Texas. The ODCB is readily nitrated to 3,4-dichloro-1-nitrobenzene which is reduced to 3,4-dichloroaniline. The 3,4-dichloroaniline is used to manufacture the herbicides and also as a dye intermediate. Dow Chemical (1975b) also cited usage of 3,4-dichloroaniline as an intermediate for polyethers and as a cross-linkage agent in epoxy tar products.

Dowtherm ® E is a heat transfer fluid (Lewis, 1975).

While ODCB is registered for use as a pesticide against termites, beetles, bacteria, slime and fungi, little is used for pesticide control at present (Lewis, 1975).

p-Dichlorobenzene

Brown et al. (1975) indicated that of a total U.S. production and consumption of 77.3 million pounds of p-dichlorobenzene per year (year not specified), 69.6 million pounds went to nonintermediate dispersive use. This figure is about 90% of production. They cited 39.0 million pounds/year [36%] used as a space odorant, and 30.6 million pounds/year [44%] used in moth control.

The consumption of p-dichlorobenzene as a pesticide is greatest in the Northeast and Northcentral regions, followed by the Southeast and Southcentral (see Table 26).

TABLE 26

PESTICIDAL* USE BY CATEGORY AND GEOGRAPHICAL REGION
(Midwest Research Institute, 1974)

Region	Agricult.	Indust/Commercial	Govt.	Domestic Uses	Total
N.E.		4[†]	0.7[†]	10[†]	14.7[†]
S.E.		2	0.3	7	9.3
N.C.		4	0.4	10	14.4
S.C.	negl.	2	0.3	7	9.3
N.W.		0.5	0.1	1.4	2.0
S.W.		1.5	0.2	3.6	5.3
Total	negl.	14.0	2.0	39.0	55.0

*As defined by Midwest Research Institute, this includes use for moth control and toilet-space deodorizing only.

[†] Quantities in million pounds.

As the above table shows, domestic uses of PDCB are by far the most important. Use of p-dichlorobenzene as a moth control agent for wool is declining as more synthetic fabrics are produced. It acts as either a repellent or a larvicide (Midwest Research Institute, 1974).

As a fungistat and insecticide, PDCB is effective in the control of mildew, tobacco blue mold, bark beetles, moths and peach tree borers (Allied Chemical Corp., 1973). p-Dichlorobenzene has also been used as a fumigant to control lice, mites and cockroaches (Dow Chemical, 1975b).

The volatility, density and pleasant odor of p-dichlorobenzene explain its use as a deodorant for toilets, garbage and diaper pails, etc. p-Dichlorobenzene is used in molding grinding wheels, as the compound readily volatilizes to leave voids in the molds (Allied Chemical Corp., 1973). PDCB is also used as a disintegrating paste for molding concrete and stoneware (Dow Chemical, 1975b).

Small amounts of p-dichlorobenzene are used to manufacture polyphenylene-sulfide resins by reaction with sodium sulfide (Dow Chemical, 1975b). As an intermediate, PDCB is diazotized to yield the dye intermediate 4-chloro-2-nitroaniline (Dow Chemical, 1975b). Hardie (1964) mentioned minor use of p-dichlorobenzene as an extreme pressure lubricant.

Trichlorobenzenes

1,2,4-Trichlorobenzene (1,2,4-TCB) is the most important of the trichlorobenzene isomers. The consumption of this isomer is shown in Table 27 for 1973.

When used as a dye carrier, 1,2,4-TCB is mixed with a disperse dye and a leveling agent, and then applied to mainly polyester materials for several hours at 100°C. The excess carrier is removed by either: (a) alkaline scour

TABLE 27

USES OF 1,2,4-TRICHLOROBENZENE, 1973
(Lewis, 1975)

Use	Millions of Pounds
Dye carrier	13
Herbicide intermediate	8
Functional fluids	5
Miscellaneous	2
Total	28

at 70° to 80°C with a sulfated fatty alcohol; or (b) after rinsing the material, it may be heated to 190°C for one minute (Lewis, 1975).

1,2,4-TCB reacts with cuprous cyanide to form 2,4-dichlorophenyl nitrile which hydrolyses to the herbicide 2,5-dichlorobenzoic acid (Dow Chemical, 1975b). It is also used to make Banrel ® (3,6-dichloro-o-anisic acid) and Phosvel ®.

1,2,4-Trichlorobenzene is a flame-retardant, stable and non-corrosive compound with "potential" as a dielectric fluid for transformers (Dow Chemical, 1975b). 1,2,4-Trichlorobenzene has degreasing properties similar to the lower chlorinated benzenes (Hardie, 1964).

This isomer has a comparatively high boiling point (210°C) and melts at 17°C. It is used as a solvent for the fractional crystallization of high melting point compounds. 1,2,4-Trichlorobenzene has insecticidal activity against termites (Hardie, 1964), but according to Lewis (1975) little of the isomer is used in termite control at present. Dow Chemical (1975b) reported use of 1,2,4-trichlorobenzene as a heat transfer medium.

A mixture of the three isomers is used for solvent purposes (Hardie, 1964). This mixture contains predominantly 1,2,4-TCB (85%) and 1,2,3-TCB (7.3%) with trace amounts of dichloro- and terachlorobenzenes. The mixture is also used as a lubricant and as a dielectric fluid (Hardie, 1964).

The 1,2,3- and 1,3,5-trichlorobenzene isomers have minor importance as intermediates in chemical syntheses.

Tetrachlorobenzenes

As shown in Figure 12, 1,2,4,5-tetrachlorobenzene is used to manufacture 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Lewis (1975) estimated that 1973 production of 2,4,5-trichlorophenol (TCP) consumed 6 million pounds of 1,2,4,5-tetrachlorobenzene, while an additional 10 million pounds went to 2,4,5-T production.

TCP can be used for the same purposes as pentachlorophenol -- as a fungicide, a disinfectant, a preservative for leather, wood and textiles (Dow Chemical, 1975b; Lewis, 1975). It is an intermediate for the preparation of both Silvex ® and Ronnel ®. Silvex ® is a herbicide and Ronnel ® is a systemic insecticide (Lewis, 1975). The sodium salt of 2,4,5-trichlorophenol reacts with monochloroacetic acid to yield 2,4,5-T, the herbicide. Since the end of the Vietnamese War, the use of this and similar herbicides has decreased.

Both 2,4,5-trichlorophenol and 2,4,6-trichlorophenol form methylene-bridged dimers with germicidal properties. Hexachlorophene, the most well-known of these dimers, is now restricted for usage in this country.

Like 1,2,4-trichlorobenzene, 1,2,4,5-tetrachlorobenzene has been used as a dielectric fluid. The isomer is also used to impregnate materials for moisture resistance and as a temporary fire-retardant protection in packaging.

Pentachlorobenzene

Pentachlorobenzene has very limited use as an intermediate. Lewis (1975) reported that the Olin Corporation purchases higher chlorinated benzenes to nitrate to the fungicide, pentachloronitrobenzene.

2. Discontinued Uses

As discussed above, certain current uses of chlorinated benzenes as intermediates are being phased-out in favor of more convenient routes to the desired end-product. The most obvious example is the gradual phasing-out of phenol production from chlorobenzene.

As previously mentioned ODCB has been replaced as a degreasing agent for aircraft engines, because of environmental concern relating to its use.

Several uses of chlorinated benzenes as chemical intermediates are in decline not because of environmental concern surrounding the chlorinated benzenes themselves, but because of the toxicity of the final product or its impurities. Production of the defoliant 2,4,5-T from 1,2,4,5-tetrachlorobenzene is in decline partly because of the a hazardous nature of the impurity, dioxan, but also because the Vietnamese war is now over.

1,2,4,5-Tetrachlorobenzene is the starting material for manufacture of 2,4,5-trichlorophenol which dimerizes to produce hexachlorophene. The use of this once widely used germicide is now restricted because of its toxicity.

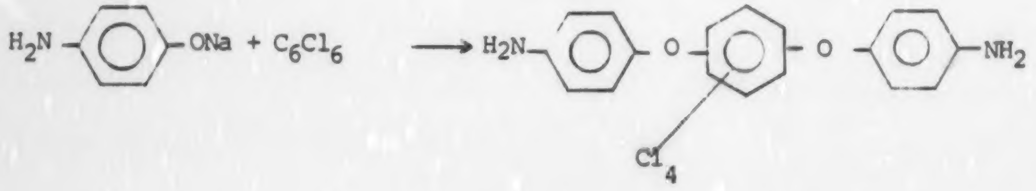
Monsanto Chemical Intermediates Co. (1977) pointed out that because of its physical characteristics, TCB has limited applications as a replacement for PCBs in dielectric fluids. Hence, as replacements are found for askarel mixtures, use of chlorinated benzenes in dielectric fluids will decline.

3. Projected or Proposed Uses

As discussed previously, expansion of certain current uses is likely to continue, while other uses are phased out. For example, use of ODCB as a solvent for toluene diisocyanate production is expected to grow.

There are several potential uses of chlorinated benzenes which might develop within the next few years. A number of halogenated benzenes have been found to Q switch the carbon dioxide laser. Izatt et al. (1974) looked at a range of compounds including monochlorobenzene, o-dichlorobenzene, m-dichlorobenzene, bromobenzene, m-difluoro-, penta- and hexafluorobenzene. Other halogenated benzenes chosen because of their absorption spectra are expected to Q switch similarly. The above listed compounds operated on a large number of lines in both the 9.6 and 10.6 bands and are all liquids at room temperature. Mode locking occurred for all vapors tested except hexafluorobenzene (Izatt et al., 1974).

Penta- and hexachlorobenzene have been mentioned as possible chloroaromatic precursors of aryl ether amines used to produce tractable polyamide-imides and polyimides, and thermosetting polyimides (Kwiatkowski et al., 1976). The chlorinated benzene (or polychlorinated biphenyl) undergoes nucleophilic condensation with p-aminophenol. For example, p-aminophenol and hexachlorobenzene react together in a ratio of 2:1 to form tetrachlorophenyl bisether diamine (see below).



Of all the diamines evaluated by Kwiatkowski, only the above compound is considered suitable as a thermoplastic intermediate. The aryl amines are stable to heat and oxygen, fire-retarding, soluble in common solvents and have reduced amine activity compared to aniline.

As research and development is still continuing for both of the above uses, it is not possible to state whether or not they are likely to develop as either major or minor uses for these chemicals.

4. Alternatives to Use

(a) As Dielectric Fluids

Some chlorinated benzenes (especially trichlorobenzene isomers) are used as dielectric fluids in capacitors and transformers in standardized mixtures with polychlorinated biphenyls (PCBs). These mixtures are called askarels and are of slightly different composition depending on whether they are used in capacitors or transformers (Interdepartmental Task Force, 1972). The mixtures are non-flammable, chemically stable, have a low vapor pressure and a high dielectric constant. The askarel mixtures for use in capacitors have a dielectric constant similar to the capacitor paper, creating a homogeneous electric field of durability and strength. Addition of TCB to the PCB mixtures lowers the viscosity of the mixture. Replacements for askarels in capacitors have received a great deal of attention specifically with regard to their PCB content. (Though capacitors are sealed, they are discarded if leaks occur.) Various replacements suggested (gas capacitors, silicones, mineral oils, etc.) have numerous disadvantages.

Gas dielectric fluids have inferior electrical properties, fluorocarbons may have toxic decomposition products, while silicones have too low a dielectric constant. No substitute for askarels with equivalent properties meeting the stringent standards of the Underwriters Laboratory has yet been found for either capacitor or transformer use. Oil transformer fluids are cheaper than askarels but cannot be used indoors because of flammability. Dry transformers may be used indoors but cost 1 1/2 times as much as askarels and are usually bulkier.

There are several disadvantages to use of askarels: (a) hydrogen chloride which is extremely corrosive is formed as a decomposition product; (b) probable toxicity of the components (both PCBs and chlorobenzenes); (c) for transformer use, askarels are expensive compared to oil ($1.80/gallon as opposed to $0.25/gallon for oil).

(b) As Heat Transfer Fluids

Chlorinated benzenes are used as heat transfer fluids because of their high heat capacity and conductivity. They are chemically and physically stable, and have a low viscosity (for free flow through the system). There are a number of other heat transfer fluids for possible use including: (a) water (disadvantages: corrosion problem, temperature limit 374°C, need for high pressure at temperatures above 100°C); (b) molten salts and metals (advantages: resistant to radiation damage, therefore useful for reactor coolants; disadvantages: corrosion, chemical or radiochemical hazards; (c) fluorocarbons (advantages: low toxicity, high thermal stability; disadvantage: cost).

(c) As Solvents

The chlorinated benzenes are used as solvents in a wide variety of processes. They are chemically stable, relatively inexpensive and will often dissolve compounds which are insoluble in other common solvents. Replacement of chlorinated benzenes when used as solvents must be considered on a process-by-process basis. It has not been possible to make this detailed evaluation in the context of the scope of this report.

However, it should be mentioned in particular that ODCB is an extremely versatile solvent which will be difficult to replace. Nevertheless, ODCB has already been replaced to some extent as a degreasing agent by Barsol ® cresylic solvents and aqueous alkalis.

(b) FLUORINATED BENZENES

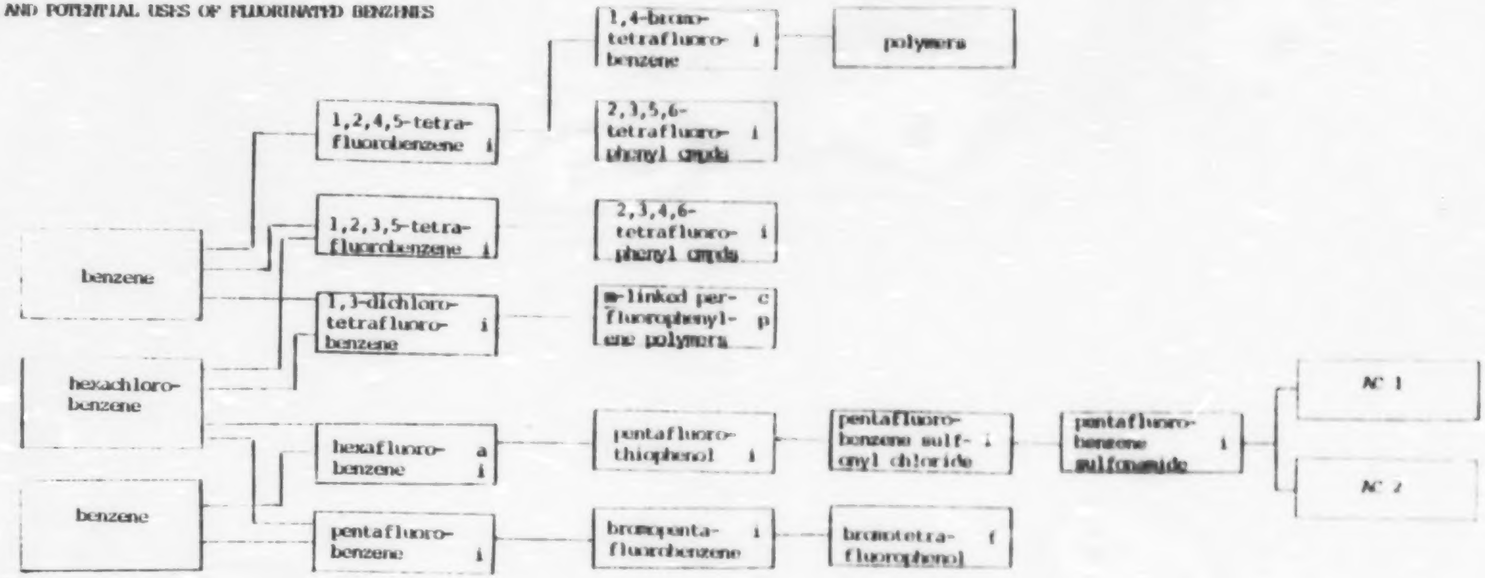
1. Major and Minor Uses, Potential Uses

The fluorinated benzenes have not been widely used as commercial chemicals in the past. New routes to the highly fluorinated benzenes have developed over the last 10 to 15 years, resulting in higher yields of previously synthesized fluorobenzenes, and first time formation of some compounds. Figure 13 summarizes the uses and potential uses of some of the fluorobenzenes. Literature references to this opening market appeared over ten years ago (Falk, 1963). From contact with current manufacturers of fluorinated aromatics, it does not appear that these uses have developed to the extent predicted in the past. The reasons for this are not clear, but are probably related to the high cost of the fluorinated benzenes, low yields in production, and/or manufacture of other chemicals with similarly desirable properties.

In any event, the following discussion of the usefulness of fluorinated benzenes and their derivatives is based on literature speculation. The potential market appears to be for the higher fluorinated compounds. While 1,2,4,5-tetrafluorobenzene, penta- and hexafluorobenzene show promise as veterinary anesthetics, their flammability in oxygen has limited development for this purpose. The hexafluorobenzene appears to be the most likely of these three to be exploited as a veterinary anesthetic (see Section IIIB).

FIGURE 13

USES AND POTENTIAL USES OF FLUORINATED BENZENES


benzene
hexachloro-benzene
benzene
1,2,4,5-tetra-fluorobenzene i
1,2,3,5-tetra-fluorobenzene i
1,3-dichloro-tetrafluoro-benzene i
hexafluoro-benzene a i
pentafluoro-benzene i
1,4-bromo-tetrafluoro-benzene i
2,3,5,6-tetrafluoro-phenyl cmpds i
2,3,4,6-tetrafluoro-phenyl cmpds i
m-linked per-fluorophenyl-ene polymers c p
pentafluoro-thiophenol i
bromopenta-fluorobenzene i
polymers
pentafluoro-benzene sulf-onyl chloride i
bromotetra-fluorophenol f
pentafluoro-benzene sulfonamide i
AC 1
AC 2

Key to Uses

a veterinary anesthesia
c coolant
f fungicide
i intermediate
p plasticizer

AC anti-convulsant
1 4-piperidino-2,3,5,6-tetrafluorobenzenesulfonamide
2 4-cyclohexylamino-2,3,5,6-tetrafluorobenzenesulfonamide

The tetra- and pentafluorophenyl compounds have a variety of uses. The bromotetrafluorobenzene forms low *p*-linked polymers when heated with activated copper powder (Barbour *et al*., 1966). Similarly, 1,3-dichlorotetrafluorobenzene forms stable *m*-linked polymers on heating with copper in dimethyl formamide for 24 hours at 154°C. Both liquid and solid polymers of great thermal stability are formed. The polymer $Cl(C_6F_4)_{16}Cl$ may be heated for 20 hours at 250°C with a weight loss of only 0.9% (Barbour *et al*., 1966). The perfluoropolyphenyls are extremely stable to both heat and radiation and have been suggested as heat-transfer fluids for nuclear power plants (Falk, 1963). The use of perfluoropolyphenyls as high-temperature fluids for military purposes has also been mentioned (Falk, 1963). Compounds of general formula: $C_6F_5(C_6F_4)\ C_6F_5$ or $C_6F_5(-X-C_6F_4)_{\overline{n}}\ X-C_6F_5$
[where X = CF_2, CF_2CF_2, CF=CF, C=O, O)
may also find use as plastics, lubricants, hydraulic and gyroscope fluids. Where n is greater than 4, boiling points are in excess of 1,000°F. The fluidity is greatest for the *m*-linked polymers.

Fluorinated phenols which contain other substituted halogens in addition to fluorine are fungicidal and could be incorporated into anti-fungal ointments (Barbour *et al*., 1966). Sulfonamides derived from pentafluorothiophenol have anti-convulsant activity. The 4-piperidino-2,3,5,6-tetrafluorobenzenesulfonamide is prepared by the reaction of pentafluorobenzenesulfonamide (I) with piperidine. Reaction of cyclohexylamine with (I) produces 4-cyclohexylamino-2,3,5,6-tetrafluorobenzenesulfonamide.

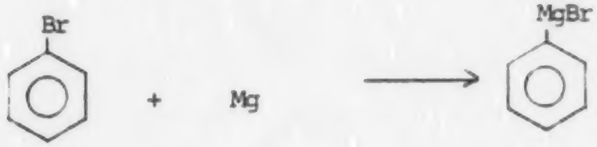
Hexafluorobenzene has been used as a solvent in scintillation counters and has potential as a solvent for proton nuclear magnetic resonance spectroscopy. Hexafluorobenzene is a very stable solvent.

Monofluorobenzene is also a solvent and an intermediate used in the preparation of insecticides and larvicides, as well as a reagent for plastic or resin polymers (Hawley, 1971).

BROMINATED BENZENES

1. Major and Minor Uses, Chemistry Involved in Use

Monobromobenzene is used as a solvent for oils, motor fuels and top-cylinder compounds (Great Lakes Chemical Corp., 1975; Hawley, 1971). Monobromobenzene is also used as a crystallizing solvent, and as an important intermediate for organic syntheses. Unlike chlorobenzene, monobromobenzene forms a Grignard reagent without difficulty and in good yields (Fieser and Fieser, 1960). Monoiodobenzene also forms a Grignard. The ability of the bromo- and iodobenzenes to form Grignards is of value in organic syntheses, as aromatic compounds generally cannot be prepared by means of a Claisen condensation (ethyl acetoacetate) or through reaction with ethyl malonate (Mann and Saunders, 1961). Grignard formation takes place through reaction of the aryl halide with dry magnesium granules in dry ether or in tetrahydrofuran (Fieser and Fieser, 1960). Addition of iodine may help start formation of the Grignard, which continues spontaneously as the solvent boils.



Although iodobenzene also easily forms the Grignard reagent, diphenyl is formed in a side reaction in appreciable quantities. Hence, bromobenzene is the preferred aryl halide (Mann and Saunders, 1961). Phenyl magnesium

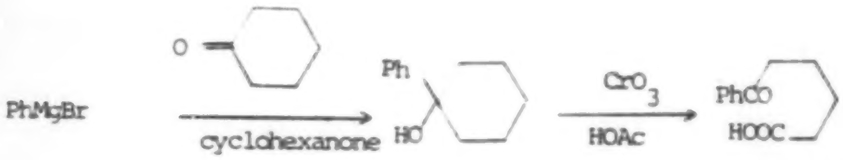
$$2\ PhI + Mg \longrightarrow Ph\text{-}Ph + MgI_2$$

bromide is seldom isolated, but reacts with additional reagents in situ to form the desired compounds.

Example

(1) Addition to a carbonyl group

(a) Phenyl magnesium bromide reacts with cyclohexanone to form the tertiary carbinol which is oxidized with chromic anyhydride and anhydrous acetic acid to form ε-phenyl-n-caproic acid, an extremely useful agent for organic syntheses (Fieser and Fieser, 1960).



ε- phenyl-n-caproic acid

(b) Phenyl magnesium bromide also reacts with ethyl benzoate to form the stable acidic triphenylcarbinol. The intermediate ketone is unstable, and immediately reacts with a second mole of the Grignard to form the carbinol.

$$C_6H_5COOC_2H_5 \quad + \quad 2C_6H_5MgBr \longrightarrow (C_6H_5)_3COMgBr \xrightarrow[91\%]{H_2O} (C_6H_5)_3COH$$

ethyl benzoate — phenyl magnesium bromide — triphenylcarbinol

Triphenylcarbinol reacts with formic acid to form triphenylmethane.

(2) Preparation of S-containing aromatics

Phenyl magnesium bromide reacts with sulfur dioxide to yield phenyl sulfenic acid ($PhSO_2H$) on hydrolysis. The phenyl sulfuryl chloride reduces with zinc dust and an acid (hydrochloric or sulfuric) to thiophenol.

(3) Addition across -C=C-

Phenyl magnesium bromide will add 1,4- across the conjugated diene system of napthacene quinone, to form a compound which goes through three additional reactions to form the polynuclear hydrocarbon, rubrene (Fieser and Fieser, 1960).

The o- and p- bromochlorobenzenes will also form mono-Grignard reagents, and are therefore important organic intermediates.

Like chlorobenzene, bromobenzene forms aryl-lithium compounds as well as reacting with sodium in the Wurtz-Fittig reaction. The Grignard reagent prepared from a bromobenzene is usually preferred to the aryl-lithium compound (though both will attack a polyfunctional carbonyl group) because the Grignard generally produces higher yields of final product.

While brominated benzenes have been used as organic intermediates as described above, the current extent of their use is not clear.

o-Dibromobenzene is used as a solvent similar to monobromobenzene, and also finds application in ore flotation techniques (Hawley, 1971). p-Dibromobenzene is useful for synthesis of dyestuffs and drugs (Hawley, 1971). Formerly, hexabromobenzene was used as a fire-retardant material for monacrylic fibres; however, it has been largely replaced by retardants which do not sublime.

(d) IODINATED BENZENES

1. Major and Minor Uses, Potential Uses, Chemistry of Use

The principal use of iodobenzene is to prepare the positive iodine compounds, the iodsyl, iodyl and iodonium salts (Hart et al., 1966). Chlorine reacts with iodobenzene in cold chloroform solution to form the moderately stable iodobenzene dichloride ($C_6H_5ICl_2$) (87 to 94% yield -- Fieser and Fieser, 1960). The dichloride reacts with caustic soda after grinding with sodium carbonate and ice to form iodosobenzene:

$$C_6H_5ICl_2 \xrightarrow[60-62\%]{NaOH} C_6H_5I^+{-}O^-$$

iodosobenzene

Iodosobenzene has been suggested as a reagent for oxidation of sulfides to sulfanes (Fieser and Fieser, 1967) but whether it is manufactured for this purpose is unclear.

On heating or on exposure to light, iodobenzene dichloride decomposes to p-chloroiodobenzene. Iodobenzene dichloride is apparently used to convert cholesterol to the 5,6-dichloride (used in the further synthesis of steroids) (Fieser and Fieser, 1967).

Reaction of iodobenzene with 30% peroxyacetic acid produces iodosobenzene diacetate ($[PhIOCOCH_3]^+CH_3COO^-$) used as a coupling agent in the preparation of diaryliodonium salts.

The iodyl (formerly iodoxy-RIO_2) compounds can be prepared from the iodosyl compounds by steam distillation (Feast and Musgrave, 1971).

$$2PhIO \longrightarrow PhI + PhIO_2$$

These compounds are of theoretical interest, but are not of industrial importance. Diphenyliodonium compounds have been prepared by reaction of iodosobenzene with phenyl magnesium bromide. Diphenyl iodonium hydroxide ($[Ph_2I]^+OH^-$) is a strong base and forms stable salts on neutralization. Though of academic interest, iodonium salts are of no commercial importance (Hart et al., 1966).

p-Diiodobenzene is a photosensitizer and has been shown to increase the speed of cross-linking of photosensitive polyacetylenes (Hawley, 1974). It is not known if p-diiodobenzene is commercially used for this purpose.

C. ENVIRONMENTAL CONTAMINATION POTENTIAL

1. General Discussion

At present, the only halogenated benzenes of great concern as environmental contaminants are the chlorinated benzenes. This is because:

(a) only the chlorinated benzenes are currently manufactured in large quantities;

(b) the use of chlorinated benzenes is widespread in this country and throughout the industrial nations;

(c) the uses of the chloro compounds are varied, and result in exposure at home and in the garden, as well as in the working environment;

(d) chlorinated benzenes have been detected in wastewaters, drinking waters, rivers and lakes as well as in the soil;

(e) at least two chlorinated benzenes have already been detected in human fatty tissues and blood. They are p-dichlorobenzene and hexachlorobenzene.

Therefore, this section will deal with chlorinated benzenes only, unless there is specific data relating to other halogenated benzenes. It should be pointed out that a number of brominated benzenes including monobromobenzene, bromochlorobenzene, and dibromobenzene have been identified in drinking water in the U.S. (EPA, 1975b)

2. Production

There are a number of reports of contamination in the industrial environment resulting in worker exposure to several of the chlorinated benzenes. Table 50 documents the effects of human exposure to mono-, o- and p-dichlorobenzene. Contact with the vapors of chlorinated benzenes may occur during their manufacture, or when used as chemical intermediates.

A recent EPA report (EPA, 1976a) gives the following breakdown for loss of chemicals to the environment during batch production of monochlorobenzene (see Table 28). These figures are based on a plant similar to that diagrammed in Figure 10. The composition of the sludge is not indicated.

TABLE 28

ESTIMATED LOSS OF MATERIALS DURING BATCH MANUFACTURE OF CHLOROBENZENE
(EPA, 1976a)

Chemical	Source	Quantity Produced (kg/kg MCB)	Destination
Hydrogen chloride	Hot scrubber vent	0.0014	Air
Monochlorobenzene	Dichlorobenzene column	0.00088	Water stream
Dichlorobenzenes (isomers not specified)	"	0.0037	"
Monochlorobenzene	Fractionating towers	0.004	Land disposal
Dichlorobenzenes	"	0.0001	"
Polychlorinated sludge*	Distillation residues	0.044	"

* Designated as "hazardous"

Pagnotto and Walkley (1965) studied industrial exposure to o- and p-dichlorobenzene (PDCB) during manufacture using the urinary metabolite, p-dichlorophenol as a measure of exposure to PDCB. During washing of PDCB crystals, Pagnotto and Walkley measured air concentrations averaging 34.0 ppm (range: 7 to 48 ppm). During shoveling and centrifuging, the average air concentration was 33 ppm (10 to 49 ppm) while urinary concentration averaged 103 mg/l (range: 54 to 233 mg/l).

During packaging, pulverizing of the crystals resulted in an average 70 mg/l (53 to 87 mg/l) in urine, and 25 ppm in air (18 to 34 ppm). At no time during PDCB manufacture, household product packaging or abrasive manufacture did urinary levels fall below 10 mg/l. Air concentrations were never less than 8 ppm.

Brown *et al*. (1975) reported a 0.9 million pounds/annum loss of *o*-dichlorobenzene during manufacture. Use of ODCB as a solvent for TDI production may be a major source of disappearance at the workplace (Lewis, 1975). Losses occur through venting and scrubber washings. During manufacture, loss of *p*-dichlorobenzene per year was estimated at 1.2 million pounds by Brown *et al*.

Additional quantified data on loss of chlorinated benzenes to the environment during production are not available. As all of the lower chlorinated benzenes are highly volatile, contamination of the working environment is very probable due to leaks in piping and inadequate venting.

3. Transport and Storage

Monochlorobenzene is classified by the U.S. Department of Transportation (DOT) as a flammable liquid (DOT, 1976). *Ortho*- and *para*-dichlorobenzene are classified as combustible liquids. Hence, special precautions must be observed during transport and storage of chlorinated benzenes. Dow Chemical has issued a transportation equipment data sheet for monochlorobenzene (MCB), *o*-dichlorobenzene, and 1,2,4-trichlorobenzene. Details of the company's transportation control technology are found in section II D below.

Monochlorobenzene is shipped in uninsulated carbon steel tank trucks or cars (Dow Chemical, 1975c) which must be clean, dry and free of odor or scale. Allied Chemical Corporation (1973) ships MCB by tank trucks, tank cars or in steel drums (500 pounds). Montrose Chemical Corp. (1972) either ships in bulk or in returnable drums. All firms ship MCB full strength.

Prior to 1974, Dow Chemical transported p-dichlorobenzene as a solid or a liquid. The solid was carried either in railroad cars or in drums (200 pounds). Now, all PDCB is shipped by Dow Chemical as a liquid in heated insulated cars (at 99.5% purity). A 96% product is also transported is the same manner. The Allied Chemical Corporation (1973) ships PDCB as a liquid by tank truck or car, as a solid in fiber drums (200, 300 pounds) or in cartons (1250 pounds). p-Dichlorobenzene is shipped by the Monsanto Company in nonreturnable combustible fiber-pack drums (200 pounds), or in tank trucks equipped with heating coils (Midwest Research Institute, 1974).

o-Dichlorobenzene is also transported full-strength in carbon steel tank trucks or tank cars, with no insulation or heating required. Alternatively, it may be packaged in returnable steel drums. The Manufacturing Chemists Association (1974) has issued a Chemical Safety Data Sheet for ODCB. The Manufacturing Chemists Association and Dow Chemical stress the importance of grounding equipment (piping, pumps, storage tanks, etc.) when handling or storing because of the danger of explosion. It is also necessary to ground equipment when handling monochlorobenzene, which is even more likely to explode than ODCB or mixtures of the two dichlorobenzene isomers (Montrose Chemical Corp., 1972).

The importance of adequate venting when handling or storing all of the chlorinated benzenes is emphasized by the manufacturers. Montrose Chemical Corp. recommends that mono-, o-, and p-dichlorobenzene be stored outside in grounded steel tanks within a diked enclosure. The enclosure should either be covered to avoid contamination of rainwater, or provision made to treat rainwater run-off to remove dissolved organics. Many local authorities require that the lower chlorinated benzenes be stored with an automatic sprinkler system.

1,2,4-Trichlorobenzene is loaded at 90° to 100°F (32° to 38°C) into stainless steel or carbon steel tank trucks or tank cars. Insulation and heating coils are required. Dow Chemical consumes all the 1,2,4,5-tetrachlorobenzene which it manufactures internally, and therefore does not publish shipping regulations for this chemical (Dow Chemical, 1977a). Monobromobenzene is shipped by Great Lakes Chemical Corp. in non-returnable lined steel drums (55 gallons).

It would appear that environmental contamination is more likely during loading and unloading of transportation and storage tanks rather than actual transport. However, there is always the possibility of faulty or damaged equipment, and because of high volatility, losses of chlorinated benzenes may occur during both transportation and storage. Elaborate safety precautions are described by all manufacturers. No quantified data are available, however, to document the extent of any loss during transportation and storage.

4. Usage

MCB and ODCB are lost to the environment through inadequate venting, scrubbers and leaking equipment, when used as solvents for TDI production (Lewis, 1975). Figures for this loss are not available. Hydrogen chloride and the polymeric low grade sludge remaining after manufacturing TDI apparently contain less than a few hundred ppm of ODCB (Lewis, 1975).

There are several reports of monochlorobenzene contamination of the working environment from Russian and Romanian sources. Rozenbaum et al. (1947) reported worker exposure to monochlorobenzene used as a solvent in the manufacture of perchlorovinyl lacquer in a plant in the Soviet Union. The equipment used was described as "outfitted by chance and which exhibited a number of substantial defects, involving a large number of manual operations performed with open equipment." Concentrations of 0.034 to 1.44 mg/l were recorded during production. The high of 1.44 mg/l was detected near the chlorinator at the end of unloading of the concentrate. Concentrations of MCB varied from 0.06 to 0.6 mg/l in the workshop where the perchlorinated concentrate was mixed with solvents and dyes.

Gabor and Raucher (1960) found an average concentration of 0.02 mg/l of monochlorobenzene in the atmosphere of a DDT manufacturing plant. The highest value detected was 0.3 mg/l. The plant investigated was new and "met present-day requirements" (Romania). Levina et al. (1966), noted that monochlorobenzene was present in the atmosphere of a monuron production plant in concentrations of 1 to 10 mg/m^3 (258 analyses).

ODCB used as a heat transfer fluid could presumably leak into the environment from faulty or damaged equipment. No description of this possibility was found in the literature.

There is apparently wide spread use of ODCB as an odor-controller for industrial wastewater treatment plants. Consequently, ODCB is entering water systems throughout the country, and is being detected in average concentrations of 2 ppm (Kopp, 1977).

As previously mentioned, 69.6 million pounds of PDCB are used annually for moth control or as a space odorant (Brown et al., 1975). Presumably each year, a similar quantity of p-dichlorobenzene sublimes into the atmosphere. Because the compound readily sublimes, it is thought unlikely to enter foods via the environment. However, as Lewis has indicated, there remains the possibility of absorption of the highly lipophilic PDCB by fatty foods, especially if they are prepared near stores of p-dichlorobenzene.

Morita and Ohi (1975) established that there is a relatively high concentration of p-dichlorobenzene in the atmosphere of the Tokyo Metropolitan Area (2.1 to 4.2 $\mu g/m^3$). They reported indoor concentrations from use as a moth repellent or space odorizer of 1700 $\mu g/m^3$ (inside wardrobe); 315 $\mu g/m^3$ (closet); and 105 $\mu g/m^3$ (bedroom). They believe that inhalation of PDCB is probably a major path of entry into the human body. Human blood samples collected contained three times as much p-dichlorobenzene as PCBs (Morita and Ohi, 1975). However, p-dichlorobenzene and polychlorinated biphenyls were present in human adipose tissue in approximately equal concentrations. Table 29 summarizes their data.

TABLE 29

CONCENTRATION OF P-DICHLOROBENZENE IN HUMAN ADIPOSE TISSUE AND BLOOD
(Morita and Ohi, 1975)

No. of Samples	Sex	Age (years)	Sample	Concentration ($\mu g/g$)
17	M,F	25-80	Adipose tissue	0.2 - 11.7
1	M	43	"	11.7
1	F	71	"	0.2
				2.3 (Average value)
6	M,F	21-35	Blood	4 - 16 mg/ml
1	F	22	"	16
1	M	24	"	4
				9.5 (Average value)

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In the past, p-dichlorobenzene was used in comparatively large quantities to control the peach tree borer. The chemical was spread around the base of the tree and could have been absorbed into the tissues of the fruit or sublimed into the environment (Hooker Chemicals and Plastics Corp., 1977).

The use of p-dichlorobenzene in toilet blocks must result in additional environmental contamination as PDCB is flushed into sewer systems throughout the country. Some p-dichlorobenzene enters the atmosphere through this usage, but considering the placing of the toilet blocks and the density of the p-dichlorobenzene vapor, most enters the wastewater stream. The appearance of chlorinated benzenes (including PDCB) in wastewater from sewage treatment plants indicates that complete biodegradation does not always take place. It is believed that trichlorobenzenes enter the environment with PCBs, when used in askarels as dielectric fluids (Veith, 1976).

5. Disposal Methods Used

The quantities and nature of waste products generated during monochlorobenzene manufacture were previously given in Table 28. In 1972, EPA estimated that 6.97 thousand short tons of solid waste were generated through production of monochlorobenzene. The estimated cost of incinerating this waste with hydrogen chloride scrubbing was given as $ 104,000. Hooker Chemicals and Plastics Corp. (1977) feels that this estimate is about 30% too low based on their own experience. Because of an anticipated decrease in monochlorobenzene production, the 1982 solid waste projection was 6.58 thousand short tons (Saxton and Narkus-Kramer, 1975).

At Dow Chemical, the polychlorinated sludge or "tetra tar" is reduced in quantity through a proprietary process to reclaim dichlorobenzenes (Midwest Research Institute, 1974). Hydrochloric acid is recycled to chlorine production. In the event of a spill of MCB, Dow Chemical recommends recovery if possible, otherwise disposal in a secure landfill (Dow Chemical, 1977b).

In the past, the Monsanto Company disposed of the polychlorinated sludge in a secure landfill on their own property. Wells surrounding the fill were periodically tested (Midwest Research Institute, 1974). The firm currently incinerates its chlorobenzene wastes. Hydrogen chloride is recovered, though small amounts escape through venting or in wash-waters.

The Montrose Chemical Corp. of California (1972) has indicated the desirability of resource recovery from mono- and dichlorobenzene wastes rather than disposal, because of the value of the product and potential pollution through waste disposal. Company officials have recommended that monochlorobenzene be covered with water and contained in dikes or sumps until recovered. Leaking or non-returnable drums should be decontaminated by steam cleaning before disposal.

Both the Manufacturing Chemists Association (1974) and Dow Chemical (1974) have recommended the incineration of ODCB wastes, and have emphasized that this must be accomplished according to local emission standards. An off-gas scrubber should be used to prevent discharge of hydrogen chloride to the atmosphere. o-Dichlorobenzene burns to form carbon oxides, hydrogen chloride, chlorine and water. No data were found describing the extent to which controlled incineration of ODCB was practiced.

The Manufacturing Chemists Association (1974) stated that ODCB should not be allowed to enter standard sewage treatment plants or chemical landfills, except under special supervision. However, chemical/physical plants using carbon adsorption can handle ODCB satisfactorily according to Hooker Chemicals and Plastics Corp. (1977). ODCB should never be deliberately discharged into the aquatic environment.

As previously mentioned, ODCB is being added to industrial wastewater treatment plants as a deodorizer and is now found in aquatic systems throughout this country (see Section F). It would appear that recommended methods of waste control technology are not being followed by some users of the product.

The appearance of lower chlorinated benzenes in textile waste effluents has received attention for some years. Murray State College, Kentucky, is conducting an on-going study to identify chemicals present in textile wastes. They have reported the presence of chlorobenzene, p-di-, and 1,2,4-trichlorobenzene in textile finishing plant effluents (Erisman and Gordon, 1975). The compounds have not yet been quantified.

The American Dye Manufacturers Institute under contract from EPA is investigating methods for treatment of textile wastes (Lewis, 1975). No additional information was obtained.

The Southeast Water Laboratory, EPA, has identified 1,2,4-trichlorobenzene in effluents from sewage plants handling textile wastes. A level of 0.46 mg/l of 1,2,3-trichlorobenzene was detected in effluents from the Long Creek, Gastonia, sewage plant. They have also detected lower chlorinated benzenes in streams near textile mills in Wallace, N.C., Dalton and Augusta, Georgia. As Lewis has pointed out, these effluents may eventually drain to coastal areas in which commercial shell fishing is important. Shellfish are soon contaminated by chlorobenzenes, thus any such drainage should be critically controlled.

Dow Chemical recommends land disposal for p-di-, 1,2,4-tri- and 1,2,4,5-tetrachlorobenzene. More specifically, p-dichlorobenzene should be contained in an "approved landfill"; 1,2,4-TCB buried "away from water supplies"; and 1,2,4,5-tetrachlorobenzene buried in a "non-crop area."

In 1972, damage approximating $380,000 worth was accrued as a result of hexachlorobenzene (HCB) contamination of cattle in Louisiana. This cost did not include losses due to delayed marketing of about 30,000 head of cattle. Air, soil and vegetation over a 100 sq. mile area were contaminated by HCB. Cows grazing in the contaminated area accumulated HCB to values as high as 1.52 ppm. The USDA action guideline for HCB in beef fat is 0.3 ppm. Levels of hexachlorobenzene up to 5,000 ppm were found in the soil. The source of this contamination was primarily volatilization of HCB from a local landfill (EPA, 1976c).

This report suggests that other chlorinated benzenes could volatize from landfills, resulting in additional environmental contamination. Such a possibility deserves further study. In the past, it was common to bury drums of contaminated or decomposed chlorinated benzenes. A considerable quantity was disposed of in this fashion and could enter ground water or the atmosphere as a result (Hooker Chemicals and Plastics Corp., 1977).

It would appear that controlled incineration of chlorinated benzenes is the most environmentally acceptable waste-management technology if resource recovery is not possible. Incineration, however, must follow state and Federal emissions guidelines.

6. Potential Inadvertent Production in Other Industrial Processes

As is made clear in Sections I and IIA, halogenated benzenes of varying degrees of substitution are found contaminating each other as inadvertent by-products (see Table 10). Therefore, whenever a specific chlorinated benzene is utilized, lower or higher chlorinated benzenes are present in varying proportions, depending on the quality of product. Any environmental contamination resulting from this use will lead to a variety of chlorinated benzenes entering the environment.

For example, pentachlorobenzene is a contaminant of hexachlorobenzene in proportions as high as 9.6% (Courtney et al., 1976). HCB now appears to be widely distributed throughout the abiotic environment, in water, in soil and probably in the atmosphere. Hexachlorobenzene has been detected in wild life (DeVos et al., 1973), in edible animal tissue and in food and feed grains (EPA, 1973; Booth and McDowell, 1975). It has also been detected in human blood (Siyali, 1972) and human body fat (Brady and Siyali, 1972). Recently, there have been European reports of pentachlorobenzene contamination coexisting with hexachlorobenzene pollution (Stijve, 1971; Greve, 1973). This may be either because pentachlorobenzene (QCB) is a contaminant of HCB, or because it is formed by the decomposition of hexachlorobenzene perhaps through photolysis. The former possibility has received the most attention.

Pentachlorobenzene is also a contaminant of pentachloronitrobenzene (PCNB) which is used as a soil fungicide. Olin Chemicals indicates that there is less than 0.2% QCB in their pentachloronitrobenzene. Pentachlorobenzene has been detected with pentachloronitrobenzene (and other impurities and metabolites) in soil and in potatoes and carrots grown in soil treated with pentachloronitrobenzene (Greve, 1973; Beck and Hansen, 1974).

It would appear that the use of pentachloronitrobenzene results in additional environmental contamination from the higher chlorinated benzenes either: (a) through presence as a contaminant in the technical PCNB, or

(b) through degradation (whether biological, chemical or photolytic).

7. Potential Inadvertent Production in the Environment

Chlorinated benzenes have been identified as degradation products of lindane metabolism by various species. In a study to determine the interaction between lindane and soil microorganisms, Tu (1975) separated and identified a number of degradation products including pentachlorobenzene. However, in field experiments with a number of crops treated with lindane, no chlorobenzenes were detected (Tu, 1975).

Kohli et al. (1976b) investigated the conversion of [^{14}C]lindane (hexachlorocyclohexane) by lettuces grown in a hydroponic culture. They reported the following chlorinated benzenes among the metabolic products of lindane: 1,2,3-trichlorobenzene, 1,2,4-trichlorobenzene, 1,2,3,4-tetrachlorobenzene, pentachlorobenzene and hexachlorobenzene.

All of the above chlorobenzenes were present in the nutrient medium but only the trichloro- and pentachlorobenzene were detected in the lettuce plants. Hexachlorocyclohexene, found in both plants and medium, was thought to be an intermediate in the formation of the chlorinated benzenes. Further degradation of chlorobenzenes resulted in formation of phenols and/or their conjugates (also present in both plants and medium).

Reed and Forgash (1969, 1970) studied the metabolism of lindane in susceptible, moderately resistant and highly resistant houseflies. Metabolites were identified by mass spectrometry and gas liquid chromatography. After topical application or injection of lindane (4μg/fly), greater amounts of 1,2,4- and 1,2,3-trichlorobenzene, 1,2,3,4- and 1,2,4,5-tetrachlorobenzene, pentachlorobenzene and iso-pentachlorocyclohexene (iso-PCCH) were formed by the highly resistant flies than the other two groups. The resistant flies also produced more 1,2,4-tri- and 1,2,4,5-tetrachlorobenzene on topical application or injection of γ-PCCH (4μg/fly) and more pentachlorobenzenes from iso-PCCH. Reed and Forgash also demonstrated that 1,2,4-trichlorobenzene, 1,2,4,5- and 1,2,3,4-tetrachlorobenzene did not appear to be metabolized further by injecting flies with each of these compounds and analyzing for metabolites.

Six chlorobenzenes have also been "tentatively" detected as products of lindane metabolism in the rabbit (Karapally et al., 1971). They are o-dichlorobenzene, 1,2,4-trichlorobenzene, tetra- and pentachlorobenzene.

Considering the world-wide use of lindane as a pesticide and with our present knowledge of lindane metabolism in various species, some chlorobenzenes must be entering the environment as lindane degradation products. The quantities are probably very small if past research is any guide (Kohli et al., 1976b). There is not enough data available to estimate quantities.

The photodecomposition of pentachloronitrobenzene may result in inadvertent production of chlorinated benzenes in the environment. In laboratory studies, irradiation of pentachloronitrobenzene at 2537 Å resulted in formation of the three tetrachlorobenzene isomers and pentachlorobenzene (Crosby and Hamadmad, 1971).

Tetrachlorobenzene was identified as a constitutent (1.2%) of the essential oils of Mississippi salt marsh grass (Juncus roemerianus) by Miles et al. (1973). It was speculated that chlorination of naturally occuring benzene compounds within the plant resulted in formation of tetrachlorobenzene. It might thus be anticipated that other salt-water plant species could contain tetrachlorobenzene or other chlorinated benzenes.

D. CURRENT HANDLING PRACTICES AND CONTROL TECHNOLOGY

1. Special Handling

Ventilation must be sufficient to control mono- and dichlorobenzenes to below their threshold limit values. When handling 1,2,4-TCB and 1,2,4,5-tetrachlorobenzene, Dow Chemical stated that "good room ventilation" is adequate for "most operations" (Dow Chemical, 1977b). Fume systems must be designed to control the accumulation of dense fumes at floor level.

If monochlorobenzene is to be handled at 75 ppm to 2% for one hour or less, a full face mask with organic vapor canister must be worn. For greater exposures, a self-contained breathing apparatus or its equivalent is used (Dow Chemical, 1977b). Handling ODCB at 50 ppm to 2% for 30 minutes or less requires a full face mask and canister. At greater concentrations or for longer periods of time, a contained breathing apparatus should be worn. No respiratory protection is normally necessary when handling p-dichlorobenzene below 75 ppm. At greater concentrations, a full face mask fitted with an organic vapor canister is used. No respiratory protection is considered necessary when using 1,2,4-TCB as long as ventilation is adequate. If respiratory protection is required when handling 1,2,4,5-tetrachlorobenzene, an approved dust respirator is used (Dow Chemical, 1977b).

Clean and protective body clothing should be worn when handling chlorobenzenes. If contact with ODCB is likely, impervious gloves must be worn. Safety glasses with sideshields should always be used; for 1,2,4,5-tetrachlorobenzene, washing facilities near the work area must be provided.

2. Storage and Transport

Monochlorobenzene is classified by the Department of Transportation (DOT) as a flammable liquid. Because of the flammability of MCB, special care must be taken to prevent ignition. All equipment used in handling during storage and transport should be grounded. Special care must be taken to prevent contact with aluminum and its alloys, rubber and plastics (Dow 1975c, 1977b).

Centrifugal or positive displacement pumps of stainless or carbon steel are used to move the liquid. Hoses may be made of seamless stainless steel, Teflon, seamless bronze, seamless steel, or neoprene. Approved gaskets are made from asbestos, Teflon, Viton or neoprene. At a minimum, chemical goggles and rubber gloves should be worn (Dow Chemical, 1975c).

Both o- and p-dichlorobenzene are classified by DOT as combustible liquids. (Note: While PDCB is a solid at room temperature, it is often transported as a liquid as described previously.) Like MCB, both dichlorobenzenes and 1,2,4-trichlorobenzene (TCB) will react with aluminum and its alloys. o-Dichlorobenzene will also react with magnesium alloys, rubber and plastics. Therefore, essentially the same materials (as listed above) may be used to construct pumps and gaskets, and similar safety should be precautions taken. All equipment involved in the loading or unloading of ODCB should be electrically grounded (Dow Chemical, 1973).

Monochlorobenzene and o-dichlorobenzene are loaded at ambient temperature, while 1,2,4-TCB is loaded at 90° to 100° F (32° to 38° C) (Dow, 1975b). Liquid p-dichlorobenzene is also loaded at elevated temperatures. During cold weather, TCB may freeze, causing special problems in handling.

3. Emergency Procedures

(a) Spill or Leak

An explosion may occur on spillage of even small quantities of mono-, o- and p-dichlorobenzene. In case of a spill or leak, the area is immediately evacuated and roped off, as efforts are made to contain the spill while working upwind (Dow Chemical, 1974, 1975a). For a small spill, every effort is made to prevent entry of the chemicals into wastewater outlets. The compounds are covered with a non-combustible material such as sand, and swept or scooped into waste bins. In the case of a larger spill or leak, the material is initially diked and the harmful vapors are contained with water fog/spray (Dow Chemical 1975a). Full protective clothing including gloves and breathing apparatus are worn while decontaminating. Local authorities must be contacted with regard to disposal of spilled chlorobenzenes.

1,2,4-Trichlorobenzene will crystallize, if spilled at temperatures below its freezing point (16.7°C). Then, it may be shovelled into waste containers. Above 16.7°C, a TCB spill is handled in the same fashion as the lower chlorinated benzenes: the liquid is contained to prevent entry into wastewater, covered with sand, and vapors contained with water fog/spray (Dow Chemical, 1975a). Again, the authorities must be contacted. While decontaminating a spill in an enclosed area, respiratory protection and a lifeline and safety harness should be worn. An attendant should be present.

(b) Fire

Before attempting to put out a fire caused by leaking chlorinated benzenes, the leak must first be shut off. Chlorinated benzenes may decompose to form products of greater flammability or toxicity (e.g. carbon monoxide, hydrogen chloride, chlorine). Small fires are extinguished using dry chemicals or carbon dioxide. In the event of large fires, water spray or foam is preferred. An advanced fire must be fought from a protected position using monitor nozzles and hose streams to cool containers exposed to the fire in order to prevent bursting. The water runoff must be diked to prevent entry into sewers, drains and water courses.

Bromobenzene has a relatively low flashpoint and is handled similarly to the chlorinated benzenes.

(c) First Aid

In the event of eye contact with halogenated benzenes, the eye is flushed thoroughly with low pressure water for at least fifteen minutes (Dow Chemical, 1974, 1975a). A physician should be called if the exposure is severe.

Skin contact is treated by thoroughly flushing with water followed by washing with soap and water (Manufacturing Chemists Association, 1974; Dow Chemical, 1974, 1975a). Contaminated clothing and shoes are immediately removed. Clothing must be well washed before being worn again. All contaminated leather goods should be destroyed.

After excess inhalation of chlorinated benzene vapors, the exposed person should initially be removed from the contaminated area. If unconscious, suitable artificial respiration should be immediately commenced. The conscious patient is administered oxygen by a person authorized to do so by a physician. While waiting for the physician, the patient should be kept quiet and comfortably warm (Dow Chemical, 1974, 1975a).

In case of accidental ingestion of chlorinated benzenes, vomiting is induced using a common emetic such as soapy water.

E. ANALYTICAL METHODS

1. Standard Methods Used

An analytical procedure adequate for determination of a given halogenated benzene in supervised laboratory studies may not be effective for samples of an unknown history. Procedures for determination in foods or living organisms such as insects or marine life may be quite different from determination of levels in substrates such as air, water or the soil.

It has been difficult to develop a generally accepted procedure for determination of halogenated benzenes in any substrate. This is because of interference from natural and synthetic chemicals sampled with the halogenated benzenes, metabolite interference, the presence of other pesticides and variation in apparatus and chemical reagents. Additionally, the residue problem surrounding the halogenated benzenes has been somewhat neglected. In designing a prodedure for determining halogenated benzenes, the reason for the analysis, the nature of the sample, and the type and extent of interference likely to be met, must all be considered. Also desirable would be a positive identification of the compound.

Confirmation of identity may be accomplished by gas chromatography/mass spectrometry techniques. However, the electron impact induced fragmentation limits the use of the mass spectrometer for structural studies, though it does give information on the number of halogen atoms. In characterizing components, other combinations of techniques have also been employed including: gas liquid chromatography (GLC) retention times on different columns; infrared spectra; and nuclear magnetic resonance spectroscopy. Thin layer and paper chromatography are also used.

Chlorinated Benzenes

Hexachlorobenzene was the first of the halogenated benzenes to cause concern as an environmental contaminant. Hence, many procedures for detection of this compound are well documented. The following methods were first used to detect HCB in cereals, animal fat and dairy products, and are also now applied to other halogenated benzenes.

(a) Preparation of Samples

There are a number of ways to prepare samples of halogenated benzenes for analysis. Four such methods are described below.

(i) Direct Steam Distillation (Stijve, 1971)

Between 10 to 20 grams of a finely ground sample are weighed and placed in a one liter round bottom flask. Distilled water (750 ml) plus pure benzene (3 ml) are added, and the flask connected to a Dean and Stark apparatus. On condensation, the distillate flows into the receiver, and the benzene fraction separates from water as a 3 cm upper layer. A system of communicating vessels returns the water to the boil flask at the same rate at which the distillate condenses. In a determination of wheat or cereals, the distillation requires four hours. Animal fats (3 to 5 g) take six hours.

or (ii) Extraction with Pentane or Hexane (Stijve, 1971)

A soxhlet apparatus is used for a four hour extraction of 10 to 25 g samples. The extract obtained is analyzed by GLC or thin layer chromatography.

or (iii) Melting and Filtration (Smyth, 1972)

Finely chopped meat fat or grated cheese (30g) is heated at 100°C to melt. Samples of the liquid fat or cheese (1g) are then analyzed. Butter (30g) is also melted at 100°C, and the clear fat is filtered through glass wool. A 1g sample is analyzed. Whole mixed egg (2g) is first extracted with hexane and anhydrous sodium sulfate. The hexane layer is filtered through glass wool and the extraction is repeated. The two filtrates are combined for analysis.

or (iv) Partitioning with acetonitrile/pertoleum ether (Yurawecz et al., 1976)

Another effective method of preparing whole eggs, milk, fish and spinach was summarized by Yurawecz *et al*. (1976). Either acetonitrile extracts of nonfatty foods, or the combined acetonitrile extracts obtained in acetonitrile-petroleum ether partitioning of isolated fats, are diluted with water. The material is then extracted with petroleum ether.

(b) Purification Techniques

Deactivated florisil (4") is added to anhydrous sodium sulfate in a chromatography tube. The column is prewetted with hexane. The sample is mixed with deactivated florisil and poured into the column. Fractions are eluted with dichloromethane: hexane (20:80) and concentrated in a Kuderna-Danish evaporator to 1 ml (Smyth, 1972).

An alternative florisil purification procedure was described by Yurawecz et al. (1976). The column is prewetted with 40 to 50 ml of petroleum ether and the concentrated sample extract (maximum volume, 10 ml) is transferred onto the column, rinsing with 5 ml petroleum ether. Fractions up to 100 ml are eluted with petroleum ether. In order to avoid loss of volatile halogenated benzenes, the eluate is concentrated to 5 to 10 ml in Kuderna-Danish concentrators equipped with Snyder distilling columns. The volume is adjusted by addition of petroleum ether so that a 3 to 8 µl aliquot is equivalent to 20 mg for a nonfatty sample, or 3 mg for a fatty sample. For volatile compounds like the chlorinated benzenes, the solvent should never be evaporated under a jet of air or nitrogen, or loss of material will occur.

(c) Gas Chromatography

The separation of hexachlorobenzene from hexachlorocyclohexane isomers was achieved by gas chromatography on a mixed liquid phase loading of 1.5% OV-17 and 1.95% QF-1 columns (Stijve, 1971). OV-17 is a phenyl substituted polysiloxane column. The "Burke column", a mixture of DC-200 silicone and QF-1 fluorinated silicone, is also used to separate chlorinated pesticides. Identity was confirmed by reverse phase thin layer chromatography on liquid paraffin impregnated alumina columns. Acetonitrile-methanol-water-acetone (4:3:2:1) was used as the mobile phase. Hexachlorobenzene was separated not only from other chlorinated pesticides, but from several chlorobenzenes as well (see Tables 30 and 31).

Of the cereals, oils, and animal fat samples analyzed by this technique by Stijve, 28% contained hexachlorobenzene in concentrations from 0.01 to 0.1 ppm. HCB was found in greatest amounts in chicken fat, which also contained pentachlorobenzene.

Smyth (1972) found HCB residues in dairy products, meat fat and eggs using gas chromatographic columns similar to thse used by Stijve. The limit of detectability in these procedures is about 0.002 ppm.

The Food and Drug Administration (FDA) has modified the procedures of Yurawecz et al. (1976) to identify early eluting industrial chemicals including halogenated benzenes found in fish tissue (Yurawecz, 1976).

The separation of a number of chlorinated and brominated benzenes and derivatives can be achieved under the following GLC parameters:

(a) Column - glass, 6' x 4 mm i.d., packed with 10% DC-200 or 10% OV-101, or 6% OV-101 on 80-100 mest Chromosorb W(HP).

(b) Temperature (°C) - column, 130°C; injector, 150°C; detector, 200°C.

(c) Carrier gas - nitrogen, flow rate adjusted to elute QCB in 8-10 min. (ca. 120 ml/min).

(d) Detector - titanium source, concentric type, operated in electron capture mode, DC voltage set to give 1/2 full scale deflection (FSD) for 0.5 ng hexachlorobutadiene.

(e) Electrometer sensitivity - 3 x 10^{-9} ampere for full scale deflection with 5 millivolt recorder.

TABLE 30

RELATIVE RETENTION TIMES OF HEXACHLOROBENZENE (HCB) AND HEXACHLOROCYCLOHEXANE (HCH) ISOMERS ON A 1.5% OV-17 + 1.95% QF-1 COLUMN AT A TEMPERATURE OF 200° C AND A N_2 CARRIER GAS FLOW OF 60 ML/MINUTE

(Stijve, 1971)

Aldrin	1.00	(reference compound)
HCB	0.47	
α -HCH	0.53	
γ -HCH	0.67	
β -HCH	0.67	
δ -HCH	0.80	
ε -HCH	0.98	

* Various stereoisomers of hexachlorocyclohexane (HCH)

TABLE 31

R_f-VALUES OF CHLORINATED INSECTICIDES AND CHLOROBENZENES IN THE SYSTEM: Al_2O_3 + 5% PARAFFIN/CH_3CN-CH_3OH-ACETONE (4:3:2:1 V/V)

(Stijve, 1971)

DDE	0.27	HCB	0.16
Heptachlor	0.37	Pentachlorobenzene	0.23
DDT	0.42	1,2,3,4-Tetrachlorobenzene	0.41
Heptachlorepoxide	0.55	1,2,4,5-Tetrachlorobenzene	0.34
TDE*	0.62	1,3,5-Trichlorobenzene	0.38
Dieldrin	0.68	1,2,4-Trichlorobenzene	0.50
Lindane	0.72	1,2,3-Trichlorobenzene	0.57
α -HCH	0.76		
β -HCH	0.84		

* 2,2-Bis(p-chlorophenyl)-1,1-dichloroethane

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Operation of the pin-cup electron capture detector as described above gives a linear response range for the early eluting chloro- and bromobenzenes, usually not above 10 to 90% FSD at the given electrometer sensitivity and higher voltage. To ensure validity of data, the quantity of residue injected must be within the linear range for that compound within the system. Quantities of sample and relative retention times are found in Table 32.

Karasek and Vassilakopulos (1971) described a rapid method for gas chromatographic separation and quantitative analyses of mixtures of benzene, chlorobenzene and the three bromochlorobenzene isomers. They used a 10 ft. stainless steel column packed with 8 wt. % Bentone-34 modified with 10 wt. % DC-200 silicone oil on 80 to 100 mesh Chromosorb W. Their method is described as taking only 14 minutes, and giving component resolutions greater than five. Methylene chloride was used as a solvent. The Carle 8000 gas chromatograph was operated isothermally in the 30° to 200°C range, so that the helium carrier flow rate and the column temperature were optimum for quick separation and quantitative analysis. Column temperature was 60°C, detector and inlet temperatures were 170°C. The size of the sample was 0.5 microliter; helium flow rate was 30 ml/min, and detector output was 1 mV. Figure 14 shows the chromatogram obtained under these conditions. Table 33 gives the retention and weight factor data for the compounds chromatographed.

Morita and Ohi (1975) identified three chlorinated benzenes in human fatty tissue by mass fragmentography and mass spectroscopy. p-Dichlorobenzene, 1,2,4,5-tetrachlorobenzene and hexachlorobenzene were all detected in levels above 0.010 µg/g fat (see Figure 16).

TABLE 32

RELATIVE RETENTION TIMES OF HALOGENATED AROMATICS WITH 10% DC-200 ON 80-100 MESH CHROMOSORB W (HP)

(Yurawecz, 1976)

FDA Standard No.	Compound	Amount Needed for 1/2 FSD (ng)	Retention time relative to pentachlorobenzene
1295	Monobromobenzene	300	0.05
244	1,3-Dichlorobenzene*	60	0.08
101	1,4-Dichlorobenzene*	110	0.08
190	1,2-Dichlorobenzene*	65	0.09
1293	1-Bromo-4-chlorobenzene	8	0.14
196	1,3,5-Trichlorobenzene*	15	0.15
195	1,2,4-Trichlorobenzene*	25	0.18
1301	1,4-Dibromobenzene	3.6	0.20
194	1,2,3-Trichlorobenzene*	9	0.22
-	3,5-Dichloroanisole	100	0.25
-	2,5-Dichloroanisole	100	0.29
-	2,4-Dichloroanisole	100	0.31
-	3,4-Dichloroanisole	100	0.31
-	2,3-Dichloroanisole	100	0.35
-	2,4,6-Trichloroanisole	100	0.39
1273	1,2,4,5-Tetrachlorobenzene*	7	0.40
1272	1,2,3,5-Tetrachlorobenzene*	7	0.40
1204	Dibromophenol	3.5	0.44
1271	1,2,3,4-Tetrachlorobenzene*	7	0.50
-	2,4,5-Trichloroanisole	10	0.68
-	2,3,5-Trichloroanisole	10	0.70
-	3,4,5-Trichloroanisole	10	0.72
1300	Tribromobenzene	6.5	0.74,0.20,2.54 †
-	2,3,4-Trichloroanisole	10	0.90
1250	Pentachlorobenzene*	1.5	1.0
-	2,3,5,6-Tetrachloroanisole	5.5	1.00
1203	2,4,6-Tribromophenol	25	1.89
-	2,3,4,5-Tetrachloroanisole	5.5	1.89
-	2,3,4,6-Tetrachloroanisole	5.5	1.04
255	BHC (Beta)*	10	2.28
80	Hexachlorobenzene*	4	2.40
280	Pentachloroanisole*	4	2.54
1305	1,2,4,5-Tetrabromobenzene	5	2.55
77	BHC (gamma)*	5	2.76

---

* Indicates compound is recovered in the 6% florisil eluate when it is analyzed by the Assocciation of Official Analytical Chemists (AOAC) method for organochlorine pesticides in non-fatty foods.

† Major peak is listed first in multicomponent mixture.

FIGURE 14 CHROMATOGRAM OBTAINED FROM 8 WT % BENTONE-34/10 WT % DC-200 SILICONE OIL COLUMN AT 160°C AND 30 ML/MIN He.

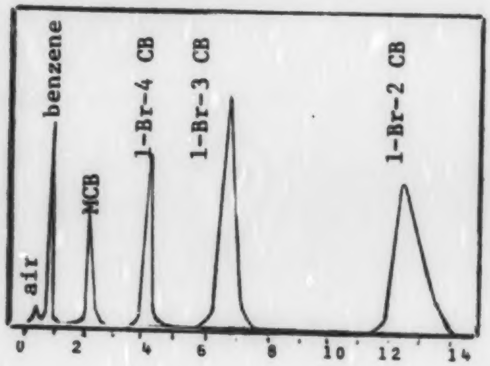

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FIGURE 15 COMPUTER PLOT OF PARENT MASS NUMBERS OF CHLORINATED BENZENES (Arrows indicate the retention times of actual samples, GLC conditions described in text) (Morita *et al.*, 1975)

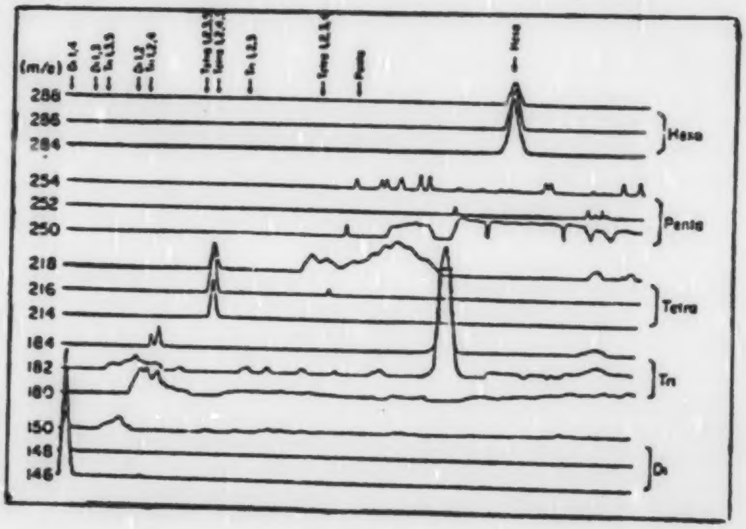

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FIGURE 16

ANALYSIS OF HUMAN FAT BY GAS CHROMATOGRAPHY/MASS SPECTROMETRY
(Sample was purified by steam distillation and H_2SO_4 treatment)
(Morita and Ohi, 1975)

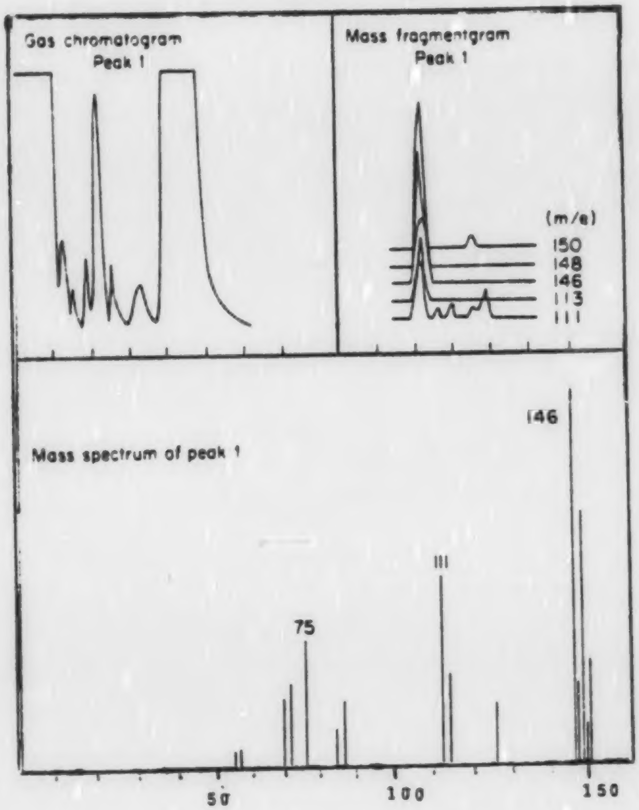

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TABLE 33

RETENTION AND WEIGHT FACTOR DATA FOR COMPOUNDS CHROMATOGRAPHED ON 8 WT. % BENTONE-34/10 WT. % DC-200 SILICONE OIL COLUMN AT 160°C AND 30 ML/MIN. CARRIER FLOW

(Karasek and Vassilakopulos, 1971)

Compound	Boiling Point °C	Weight Factors	Retention Time (Sec)	Capacity Ratio*	Resolution†	Retention Index
Air			28.6			
Benzene	80.1	1.00	57.2	1.0		837
Monochlorobenzene	132.0	1.06	131.4	3.6	7.78	1077
1-Br-4-ClBz	196.0	1.46	254.5	7.9	7.15	1227
1-Br-3-ClBz	196.0	1.44	419.0	13.7	5.48	1326
1-Br-2-ClBz	204.0	1.62	793.7	26.7	703	1451

*$k_i = (t_i - t_a)/t_a$

† $R = [2(t_j - t_i)]/(w_j + w_i)$

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Materials for analysis were prepared by a combination of steam distillation and treatment with sulfuric acid. This step was omitted for analysis of penta- and hexachlorobenzene as it did not give good recovery. Column packings were Bentone 34(5%) + DC-200(5%) on Chromosorb W, AW-DCMS (60 to 80 mesh) and Dexsil 300 G(3%) on Chromosorb W, AW-DCMS (60 to 80 mesh). The detector was ECD(Ni^{63}). The carrier gas was nitrogen flowing at 60 ml/minute. The temperature of the detector was 200°C, as was the injection temperature. For analysis of lower chlorinated benzenes, the column temperature was lower. A computer plotting of results is shown in Figure 15.

Morita and Ohi (1975) also detected p-dichlorobenzene in blood using similar procedures. Blood samples were prepared as for the fatty tissues (i.e. steam distillation, hexane extraction, sulfuric acid) except that before injection the n-hexane layer was condensed with a Kunderna-Danish evaporator.

The National Institute of Occupational Safety and Health (NIOSH) has published analytical methods for detection of chlorobenzene and o-dichlorobenzene in air (Stanford Research Institute, 1975b, 1975c). A known volume of air is drawn through a charcoal trap and the adsorbed organic vapors are eluted with carbon disulfide. An aliquot of the desorbed sample is injected into a gas chromatograph equipped with a flame ionization detector.

For chlorobenzene detection, the column (10 ft. x 1/8 in. stainless steel) is packed with 10% FFAP on 80 to 100 mesh, acid washed DMCS Chromosorb W. Nitrogen gas flow is typically 50 ml/minute (60 psig) and hydrogen gas flow to the detector is 65 ml/minute (50 psig). Air flow to the detector is 500 ml/minute (50 psig). Injector temperature is 190°C, manifold temperature is 250°C and volume temperature is 105°C.

This method was validated over the range of 183 to 736 mg/mm at 25°C and 761 mm Hg for a 10 liter sample. It is probably useful for detection of 35 to 1035 mg/m^3, though it may be capable of measuring smaller amounts if the desorption efficiency is adequate. At high humidity, or when several other compounds are also present, especially those with the same or close retention time, there is interference with the determination. The Coefficient of Variation (CV) for the complete sampling and analytical method in the range of 183 to 736 mg/m^3, was 0.056. This corresponds to a standard deviation of 19 mg/m^3.

For o-dichlorobenzene analysis, the sample is injected onto a column packed with 10% OV-101 on 100 to 120 mesh Supelcoport. Nitrogen flow is typically 30 ml/minute (60 psig) and hydrogen gas flow is 35 ml/minute (25 psig). Injector temperature is 225°C, temperature of manifold is 250°C and of the column 140°C.

This method was validated over the range 150 to 629 mg/mm. The precision of the determination (CV_t) = 0.067. This corresponds to a standard deviation of 20 mg/m^3.

Fluorinated Benzenes

Seiler and Sams (1972) studied the separation of selected polyfluorinated benzenes by gas liquid chromatography. p-Difluorobenzene, 1,2,4- and 1,3,5-trifluoro-, 1,2,4,5- and 1,2,3,5-tetrafluoro-, pentafluoro- and hexafluorobenzene were separated using a 15% Carbowax 20M Chromosorb W column. Other columns tried were not effective in separating monofluorobenzene, though some were effective in separating other halogenated benzenes. The retention behavior on Carbowax columns is shown in Figure 17, and certain physical properties are found in Table 34.

MacBeath et al. (1969) examined the photochemistry of the vapor phase of monofluorobenzene between 2350 and 2710 Å. The sensitized emission of biacetyl was used to detect both the singlet and the triplet state yields for exciting wave lengths of 2470, 2550, 2590 and 2670 Å. The effect of cyclohexane on yield was also studied. Addition of cyclohexane to monofluorobenzene increased the fluorescent yield for an excitation wavelength of 2470 Å, but did not alter the yield for the other wavelengths examined. The results were:

Compound	Excitation λ	Sum of the Φ Singlet and Φ Triplet State Yields
Monofluoro-benzene	2470 Å	0.67
	2550	0.75
	2590	0.93
	2670	0.82

Durham (1969) examined *o*- and *p*-difluorobenzene by similar spectrofluorometic techniques. He obtained the following values:

Compound	Excitation λ	Sum of the Φ Singlet and Φ Triplet State Yields
o-Difluorobenzene	2500 Å	0.34
	2580	0.52
	2660	0.75
	2770	0.97
p-Difluorobenzene	2660	0.50
	2740	0.50
	2760	0.70

TABLE 34

PHYSICAL PROPERTIES OF SELECTED POLYFLUOROBENZENES
(Seiler and Sams, 1972)

Material	Boiling Point (°C/760 Torr)	Electric Dipole moments (Debye) by the Law of Cosines of Ferguson
Benzene	80.6	0
1,4-Difluorobenzene	88.5	0
1,2,4-Trifluorobenzene	88.5	1.5
1,3,5-Trifluorobenzene	75.5	0
1,2,4,5-Tetrafluorobenzene	88	0
1,2,3,5-Tetrafluorobenzene	83	2.55
Pentafluorobenzene	80.5	1.5
Hexafluorobenzene	80.5	0

Some data extrapolated from Branch, G.E.K. and M. Calvin. The Theory of Organic Chemistry, p. 135, as cited by Ferguson, L.N., The Modern Structural Theory of Organic Chemistry. Prentice-Hall, Englewood Cliffs, N.J., 1964, p. 204.

FIGURE 17 CHROMATOGRAM OF AN AUTHENTIC MIXTURE OF FLUOROBENZENES ON A 10 FT. 15% CARBOWAX 20M ON 60-80 MESH CHROMOSORB W AT 70°C, He 33CM^3/MIN. (Seiler and Sams, 1972)

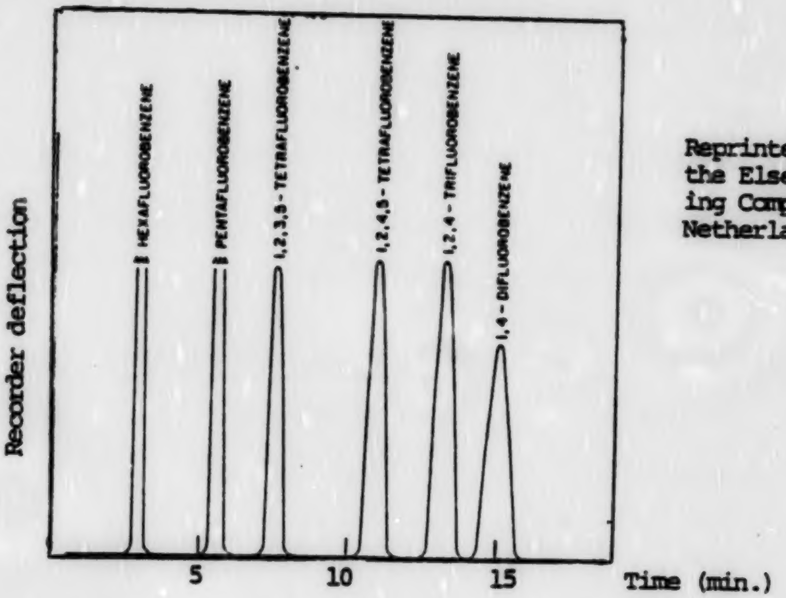

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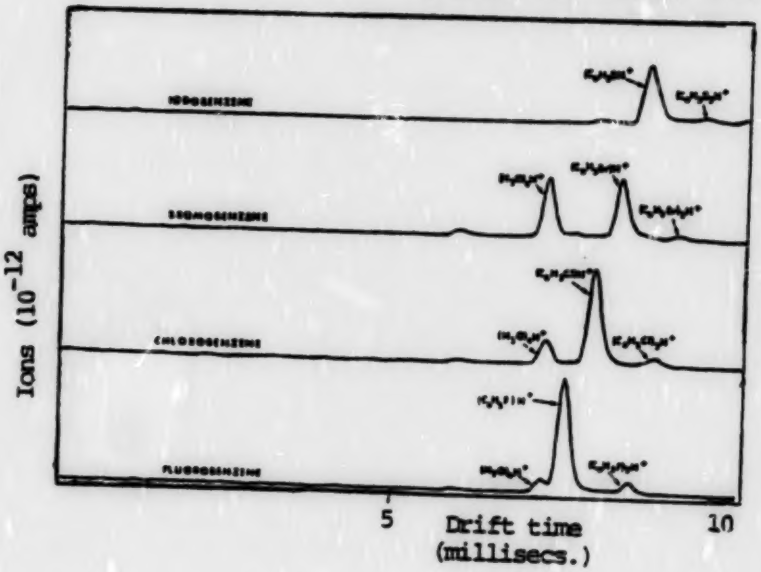
FIGURE 18 COMPOSITE POSITIVE PLASMAGRAMS OF MONOHALOGENATED BENZENES (Karasek and Tatone, 1972)



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The difluorobenzenes were shown to undergo photoisomerization, and an oxygen effect was also present.

Brominated Benzenes

Kolbasina and Lulova (1976) developed a method for the separation of bromobenzenes using gas chromatography. The 3 cm long columns were run at 180°C filled with Bentone-245 on Spherochrome 1 (0.3 to 0.4 mm particle size) with a helium flow rate of 33 ml/minute. o-Dibromobenzene had a longer retention time than the para isomer.

Nakada et al. (1970) used the following columns: silicone-SE-30 (4 mm x 2 m) isothermal at 120° and 160°; and Bentone-34 (4 mm x 2 m) isothermal at 100° and 160°C. Each temperature increase was programmed. The chromatographic patterns of bromine and chlorine derivatives were similar. The following chlorinated and brominated benzenes were measured: monohalogenated benzenes; 1,4-, 1,3-, and 1,2-dihalobenzenes; 1,3,5-, 1,2,4-, 1,2,3-trihalobenzenes; 1,2,4,5-tetrahalo-; 1,2,3,5- and 1,2,3,4-tetrabromobenzene; pentabromobenzene; and hexahalobenzenes.

Separation of Monohalogens

Karasek and Tatone (1972) studied detection of the monohalobenzenes by a technique called plasma chromatography. This technique gives data for analysis of fundamental ion-molecule reactions. Also, it provides mechanisms for the gas chromatographic electron capture detector and stable ion species observed in mass spectra. Experimental conditions are shown in Table 35. Figure 18 shows separation of the monohalogens.

Using thermal electrons and positive reactant ions from nitrogen gas, both positive and negative chromatograms of the monohalogenated benzenes were obtained. In general, positive chromatograms showed protonated molecular

TABLE 35

EXPERIMENTAL PARAMETERS FOR PLASMAGRAMS RUN FOR COMPOUNDS STUDIED

Sample temperature:	127° C
Reactant gas flow:	100 cc of dry N_2/minute
Drift gas flow:	450 cc of dry N_2/minute
Ion-molecule reaction space:	6.0 cm
Ion-drift space:	6.0 cm
Electric field:	250 V/cm
Injection pulse:	0.1 millisecond
Gating pulse:	0.1 millisecond
Recorded scan:	2 minutes
Electrometer sensitivity:	10^{-12} A full scale
Compounds:	CP reagent grade with greater than 99% purity
Gas:	Nitrogen-Linde high purity grade (99.996%), dried by metal trap of 2.25-liter capacity, packed with Linde Molecular Sieve 13X

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ions containing one or two molecular species. Negative chromatograms had a strong halogen peak, except for monofluorobenzene.

TABLE 36

DRIFT TIME AND STRUCTURE ASSIGNMENTS OF CHARGED SPECIES OBSERVED IN PLASMAGRAMS OF HALOGENATED BENZENES

Compound	Ions	Drift time (milliseconds)
Nitrogen (reactant gas)	$(H_2O)_2H^+$	5.75
	$(H_2O)_2NO^+$	6.47
	$(H_2O)_4H^+$	7.11
	Electrons	Continuum
Monofluorobenzene	$(C_6H_5F)H^+$	7.39
	$(C_6H_5F)_2H^+$	8.44
Monochlorobenzene	$(C_6H_5Cl)H^+$	7.81
	$(C_6H_5Cl)_2H^+$	8.60
	Cl^-	5.47
Monobromobenzene	$(C_6H_5Br)H^+$	8.12
	$(C_6H_5Br)_2H^+$	9.00
	Br^-	6.13
Monoiodobenzene	$(C_6H_5I)H^+$	8.59
	$(C_6H_5I)_2H^+$	9.94
	I^-	6.40
Carbon tetrachloride	Cl^-	5.42
n-Butyl chloride	Cl^-	5.42
	$(C_4H_9Cl)^-$	6.10

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TABLE 37

METHODS FOR THE SEPARATION AND DETECTION OF HALOGENATED BENZENES

Compound	Method of detection	Sample	Reference
Monochlorobenzene	u.v. absorption spectra	Air	Kisarov *et al.*, 1962
Monochlorobenzene	GLC flame ionization	Air (sensitive to 2 mg/m^3)	Sumbayev and Rakhybenko, 1975
Monochlorobenzene	GLC equilibration method	Air	Selucky *et al.*, 1967
Monochlorobenzene	Plasma chromatography	Lab. mixture	Karasek *et al.*, 1974
Monochlorobenzene Monobromobenzene All dichlorobenzenes All dibromobenzenes All trichloro- and tribromobenzenes All tetrachloro- and tetrabromobenzenes Penta- and hexachlorobenzene	GLC, i.r. spect.	Lab. mixture	Nakada *et al.*, 1970
p-Dichlorobenzene	GLC/MS	Human adipose tissue	Morita and Ohi, 1975
1,2,4,5-Tetrachlorobenzene	Mass fragmentography	Human blood, air	Morita *et al.*, 1975
Dichlorobenzenes	GLC/MS	Human blood, water	Dowty *et al.*, 1975
Dichlorobenzenes	GLC/thermal conductivity	Lab. mixture	Habboush and Tameesh, 1970
Dichlorobenzenes Trichlorobenzenes Tetrachlorobenzenes	GLC/flame ionization, TLC	Lab. mixture	Yasuda, 1973
Pentachlorobenzene	GLC/MS	Feed, animal fat, poultry products	Greve, 1973
Hexachlorobenzene	GLC/EC	Wheat	Levi et al.,
Hexachlorobenzene	GLC/EC, reverse phase TLC	Cereals, dairy products, fat	Stijve, 1971
Hexachlorobenzene	GLC/EC	Fatty foods	Smyth, 1972
Hexachlorobenzene	High pressure liquid chromatography, reverse phase TLC	Monkey feces	Yang *et al.*, 1975
Hexachlorobenzene	GLC/EC, TLC	Human body fat	Brady and Siyali, 1972
Hexachlorobenzene	GLC/EC	Human body fat	Curley *et al.*, 1973
Monobromobenzene Monochlorobenzene *o*-Dichlorobenzene *p*-Dichlorobenzene 1,2,4-Trichlorobenzene Tetrachlorobenzene	Formation of polymethine dyes	Air	Belyakov *et al.*, 1972
1,2,4,5-Tetrabromobenzene	GLC	Pesticide residues	Bache *et al.*, 1968
2-Iodochlorobenzene	Plasma emission detector		
1,4-Difluorobenzene 1,2,4-Trifluorobenzene 1,3,5-Trifluorobenzene 1,2,4,5-Tetrafluorobenzene 1,2,3,5-tetrafluorobenzene Pentafluorobenzene Hexafluorobenzene	GLC-thermal conductivity	Lab. mixture	Seiler and Sams, 1972

F. MONITORING EFFORTS

A number of chlorinated and brominated benzenes have been detected in raw water and drinking water throughout the U.S. The National Organic Reconnaissance Survey (EPA, 1975b) analyzed raw water sources of five basic types to determine their organic chemical content. A summary of their findings with location and type of water source is included in Table 38.

Two analytical techniques are indicated in this same table. Volatile organic analysis (VOA) involves aeration of the water sample with an inert gas to purge organic contaminants. In the carbon/chloroform technique, organic contaminants are adsorbed onto activated carbon and eluted with chloroform. The VOA figures have been corrected for recovery efficiencies, but the carbon-chloroform data have not, and are therefore possibly low (EPA, 1975b).

Monochlorobenzene was detected in nine of the ten cities surveyed for this study: in ground water, in "uncontaminated" upland water, and in waters contaminated by either industrial, municipal or agricultural wastes.

The work by Erisman and Gordon (1975) is still in progress. The data made available for this report are included in Table 38 but are not yet quantified. Mono-, p-di- and 1,2 4-trichlorobenzene were all detected in textile waste effluents.

Dichlorobenzene (isomer not specified) was detected in wastewaters from Lakeway Chemical, Inc., in Muskegon, Michigan (Christensen and Long, 1976). Monitoring of wastewaters took place during one 24-hour period starting July 12, 1976. Lakeway Chemical produces a lauryl alcohol base detergent, dye intermediates, pesticides and herbicides. During the monitoring period, only the detergent plant was operational.

Process cooling and domestic water used within the plant were discharged without treatment to the sewage system. (Process water from the pesticide and herbicide plants was not discharged, but hauled away by licensed haulers.) Cooling water from the different plants was recycled through cooling towers or a spray pond. It was treated with Dearborn 726 and/or calcium hypochlorite. Overflow from either towers or ponds was retained in a seepage lagoon behind the plant. Other seepage lagoons for retaining process water are no longer in use, but have drained to a residual sludge. Because the soil is sandy, wastewaters quickly seep through to discharge into a swampy area draining into Big Black Creek.

Grab samples were taken from the east and west seepage areas, from cooling water, and up and downstream along Big Black Creek. Continuous samples were collected from the Creek, up and downstream, by displacement of air from a submerged container. The quantity of each contaminant discharged daily was calculated from:

$$\text{lb/day} = \text{flow (mg/d)} \times \text{conc. (mg/l)} \times \text{unit weight of the water (8.34 lb/gal)}$$

Flow rate was determined during continuous monitoring of the Creek. The report did not give the analytical techniques used to determine the various wastewater constituents. Quantities of dichlorobenzene of just under 10 µg/l were detected in both seepage and cooling waters.

The plant produces dichlorobenzidine-dihydrochloride from o-nitrochlorobenzene. This process might be responsible for the appearance of dichlorobenzene in wastewaters of the plant.

TABLE 38 MONITORING FOR CHLORINATED BENZENES IN WATER SYSTEMS

Concentration (μg/l)	Location	Source	Analytical Methods	Reference
(a) Monochlorobenzene:				
d	Miami, Florida	Ground water	Volatile organic analysis (VOA)	EPA, 1975b
d	"		"	
1.0	"		Carbon/chloroform extract	
d	Seattle, Washington	"Uncontaminated" upland water	VOA	
d	Ottumwa, Iowa	Raw water contaminated with agricultural run-off	VOA	
d	Philadelphia, Pennsylvania	Raw water contaminated with municipal waste	VOA	
0.1		"	VOA	
d		"	VOA	
d	Cincinnati, Ohio	Raw water contaminated with industrial discharges	Carbon/chloroform extract	
0.1	"		VOA	
0.5	"		VOA	
4.7	New York, New York	"Uncontaminated" upland water		
0.12	Lawrence, Mass.	Raw water contaminated with industrial discharges		

d - detected by 500 ml VOA but not quantified. Limits of sensitivity not indicated.

TABLE 38 (Continued)

Concentration (µg/1)	Location	Source	Analytical Methods	Reference
d	Grand Falls, North Dakota	Raw water contaminated with agricultural runoff	VOA	EPA, 1975b
5.6	Terrebone Parish, Louisiana	Raw water contaminated with municipal waste	VOA	"
d	not indicated	Textile plant effluents	Not indicated	Erisman and Gordon, 1975
(b) o-Dichlorobenzene:				
1.0	Miami, Florida	Ground water	Carbon/chloroform extract	EPA, 1975b
d			VOA	
d	Philadelphia, Pa.	Raw water contaminated with municipal waste	VOA	
d	Cincinnati, Ohio	Raw water contaminated with industrial discharge	VOA	

d - detected by 500 ml VOA but not quantified. Limits of sensitivity not indicated.

TABLE 38 (Continued)

Concentration (µg/1)	Location	Source	Analytical Methods	Reference
(c) m-Dichlorobenzene:				
0.5	Miami, Florida	Ground water	Carbon/chloroform extract	EPA, 1975b
d			VOA	
d	Philadelphia, Pa.	Raw water contaminated with municipal waste	VOA	
d	Cincinnati, Ohio	Raw water contaminated with municipal waste	VOA	
d	Lawrence, Mass.	Raw water contaminated with industrial discharge	VOA	
(d) p-Dichlorobenzene				
0.5	Miami, Florida	Ground water	Carbon/chloroform extract	EPA, 1975b
d			VOA	
d	Philadelphia, Pa.	Raw water contaminated with municipal waste	VOA	
d	Cincinnati, Ohio	Raw water containing industrial discharge	VOA	

d - detected by 500 ml VOA but not quantified. Limits of sensitivity not indicated.

Table 39 lists the halogenated benzenes detected in drinking water in the U.S. The list was compiled from Environmental Protection Agency reports and through examination of the literature. It should not be considered a complete listing. Table 40 gives details of monitoring efforts in Region IV EPA.

TABLE 39

HALOGENATED BENZENES FOUND IN DRINKING WATER IN THE U.S. (EPA, 1975b)

Chemical	Highest Reported Concentration (μg/l)*
Monobromobenzene	
Bromochlorobenzene	
Monochlorobenzene	5.0
Dibromobenzene	
o-Dichlorobenzene	1.0
m-Dichlorobenzene	3.0
p-Dichlorobenzene	1.0
Hexachlorobenzene	
Trichlorobenzene	1.0

*Sample site and concentration range were not indicated.

Young et al. (1976) are conducting a major monitoring effort to detect and quantify chlorinated benzenes in major municipal wastewaters of southern California. Hexachlorobenzene was first detected by electron capture gas chromatography while investigating levels of PCBs and other chlorinated pesticides. During two seasonal surveys in 1975, Young et al. detected other chlorinated benzenes in the wastewaters. Their concentrations were comparable to PCB levels and in excess of HCB values by at least an order-of-magnitude.

The samples were collected from submarine outfalls of effluents from the Joint Water Pollution Control Plant (JWPCP), the Hyperion Sewage Treatment Works, L.A. (5 mile and 7 mile effluents); the Orange County Sewage Department (OCSD); and Port Loma and Oxnard Sewage Treatment Plants.

TABLE 40

CHLORINATED BENZENES IDENTIFIED IN THE ENVIRONMENT IN REGION IV (EPA, 1977a)

Compound	State	Receiving Water	Sample Type	Concentration (mg/l)*	Method of Detection	Date
HCB	KY	Ohio River	Industrial discharge	0.011	Hall electrolytic conductivity detector	74/7
	KY	"	"	unknown	-	71/7
	KY	"	"	0.05†	Mass spectrometer	75/8
TCB	GA	Coosa River	Municipal discharge	0.005†	Mass spectrometer	76/2/25
	NC	Catawba Creek	"	0.041	Flame ionization detector	
	NC	Catawba Creek	"	0.019	"	73/7
ODCB	NC	Catawba River	Industrial discharge	0.69	Flame ionization detector	73/7
	TN	Big Bigby Creek	"	0.04†	"	74/9/18
	KY	none	Ground water	0.071	Hall electrolytic conductivity detector	76/5/19
	KY	unknown	Industrial waste holding pond	0.015	"	76/6/3

*Qualified value — same as the true value but no recovery studies were performed. True value compares response of compound in sample to standard compound. Recovery data for the compound spiked in distilled water is 70% or greater. Values not corrected for recovery.

†Estimated concentration based on relative response of standard compound vs. organic compounds similar to standard. Also, no sample preparation recovery data are available.

TABLE 40 (continued)

Compound	State	Receiving Water	Sample Type	Concentration (mg/l)*	Method of Detection	Date
ODCB	KY	none	Ground water	0.0012	Hall electrolytic conductivity detector	76/6/3
1,2,3-TCB	NC	Catawba Creek	Municipal discharge	0.021	Flame ionization detector	73/7
	NC	"	"	0.046	"	73/7
1,2,4-TCB	NC	Catawba River	Industrial discharge	0.012	Flame ionization detector	73/7
	TN	Chattanooga Cr.	"	0.5†	"	73/3
	TN	Chattanooga River	Municipal discharge	unknown		73/3
1,3,5-TCB	TN	Holston River	Industrial discharge	0.026	Hall electrolytic conductivity detector	74/9/26
PDCB	TN	Big Bigby Creek	Industrial discharge	0.058	Flame ionization detector	74/9/18

*Qualified value — same as the true value but no recovery studies were performed. True value compares response of compound in sample to standard compound. Recovery data for the compound spiked in distilled water is 70% or greater. Values not corrected for recovery.

†Estimated concentration based on relative response of standard compound vs. organic compounds similar to standard. Also, no sample preparation recovery data are available.

TABLE 40 (continued)

Compound	State	Receiving Water	Sample Type	Concentration (mg/l)*	Method of Detection	Date
MCB	SC	Lawsons Fork Creek	Industrial Discharge	0.008	Flame ionization detection	76/5/27
	SC	"	"	0.017	"	76/5/23
	GA	Coosa River	Municipal	0.027 †	Mass spectrometer	76/2/25
Dichloro-benzene	SC	Lawsons Fork Creek	Industrial Discharge	0.032	Flame ionization detection	76/5/27
	TN	Big Bigby Creek	"	unknown	"	75/1/26
	SC	Lawsons Fork Creek	"	0.012	"	76/5/23
	NC	Catawba River	"	0.033	"	73/7
	KY	unknown	Industrial waste holding	0.0009 †	Hall electrolytic conductivity detector	76/6/03
	KY	none	Ground water	0.012 †	"	76/5/19
	KY	none	Ground water	0.0012 †	"	76/6/3

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*Qualified value — same as the true value but no recovery studies were performed. True value compares response of compound in sample to standard compound. Recovery data for the compound spiked in distilled water is 70% or greater. Values not corrected for recovery.

†Estimated concentration based on relative response of standard compound vs. organic compounds similar to standard. Also, no sample preparation recovery data are available.

Table 41 gives the estimated chlorinated benzene content of wastewaters analyzed during these two surveys.

In 1976, large grab samples were collected from JWPCP, OCSD and Hyperion 5 and 7 mile sludge effluents. Replicate sets (volumes 1,10 and 10 1) were extracted and processed. Each sample was independently analyzed by: (1) the Southern California Coastal Water Research Project Authority; (2) California Analytical Laboratories (CAL) in Sacremento; and (3) EPA Environmental Research Laboratory in Athens, Georgia.

The CAL samples were analyzed by mass fragmentography. Confirmation of identity of the compounds was made on the basis of retention time and detection of molecular ions. 1,3,5-TCB was not confirmed. The Athens laboratory also determined the presence of chlorinated benzenes in the samples. Table 42 gives the data as analyzed by CAL. It agrees well with data contained in the previous table.

TABLE 41

MUNICIPAL WASTEWATER CHLOROBENZENE CONCENTRATIONS (μg/1) DETERMINED BY ELECTRON-CAPTURE GAS CHROMATOGRAPHY (gc/ec) AND MASS SPECTROMETRY (gc/ms) (Young *et al*., 1976)

Chloro-benzene	JWPCP		Hyp. 7-mi.		OCSD	
	gc/ec	gc/ms	gc/ec	gc/ms	gc/ec	gc/ms
PDCB	7.6	7.4	90	7.8	2.8	-
ODCB	5.1	3.3	183	14	1.3	-
1,2,4-TCB	0.58	0.54	86	34	0.08	-
1,3,5-TCB	< 0.01	-	0.3	-	0.001	-
HCB	0.10	0.05	0.45	0.41	0.010	0.007
Total chlorinated benzenes	13	11	360	56	4.2	-

TABLE 42

ESTIMATED CHLOROBENZENE CONCENTRATIONS (µg/1) IN MAJOR MUNICIPAL WASTEWATERS
(Young *et al*., 1976)

Chlorobenzene	JWPCP *		Hyp-5 mi †		Hyp-7 mi ‡		OCSD §		Pt. Loma		Oxnard	
	Sum.	Fall	Sum.	Fall	Sum.	Fall	Sum.	Fall	Sum.	Fall	Sum.	Fall
PDCB	7.4	12	3.4	5.1	34	230	4.9	-	-	0.42	9.3	3.1
ODCB	7.3	12	1.9	4.0	30	440	2.4	-	2.2	< 0.01	4.7	2.3
1,2,4-TCB	6.0	1.8	5.7	3.1	275	130	0.3	-	0.23	< 0.01	0.9	0.25
1,3,5-TCB	0.2	0.8	<0.01	< 0.01	0.9	< 0.2	0.02	-	0.02	< 0.01	0.4	< 0.01
HCB	0.4	0.2	0.07	0.01	1.9	6.8	0.04	-	0.01	< 0.01	0.4	0.04
Total Chlorinated Benzenes	21	27	11	12	340	800	7.7	-	2.5	0.4	16	5.8

* Joint Water Pollution Control Plant
† Hyperion Sewage Treatment Works - 5 mile effluents
‡ Hyperion Sewage Treatment Works - 7 mile effluents
§ Orange County Sewage Department

Young *et al*. found that surface runoff of chlorinated benzenes into the Los Angeles River is of much less significance as a source of marine pollution than are wastewater effluents. Table 43 gives data from a sampling of the river following a major storm in February 1976. Samples were collected over a four day period using an all metal depth-integrating sampler. While input of chlorinated benzenes into the Bight via the Los Angeles River runoff was comparatively low, this River is the single most important route for entry of other chlorinated hydrocarbons into coastal waters of the area (Young *et al*., 1976).

TABLE 43

SURFACE RUNOFF OF CHLORINATED HYDROCARBONS, LOS ANGELES RIVER, FEB. 1976
(Young *et al*., 1976)

Chlorinated Hydrocarbon	Net. Conc. (µg/l)	Md. Blank (µg/l)
PDCB	0.05	0.03
ODCB	0.01	0.01
1,2,4-TCB	0.007	0.003
1,3,5-TCB	0.006	0.001
HCB	0.001	< 0.001
Total DDT	0.33	< 0.004
Aroclor 1254	0.47	0.004
Aroclor 1242	< 0.18	0.005

In order to determine the importance of aerial fallout of chlorina benzenes, high volume air samples were collected from five stations in Los Angeles Basin. Results are summarized in Table 44.

TABLE 44

AERIAL FALLOUT OF CHLORINATED HYDROCARBONS OFF SOUTHERN CALIFORNIA — SPRING 1976 (ng/m^2-day)

(Young *et al.*, 1976)

Chlorinated Benzene	El Segundo*	Catalina Island	San Clemente Island	La Jolla	Santa Barbara	Median
PDCB	-	-	-	-	-	-
ODCB	-	< 8	27	-	< 53	< 27
1,2,4-TCB	< 20	-	< 3	< 2	< 19	< 11
1,3,5-TCB	-	< 1	< 3	< 10	< 8	< 6
HCB	0.9	1.7	0.1	3.4	0.9	1
Total DDT	640 †	73	280	30	820	280
Aroclor 1254	860	230	98	98	78	170
Aroclor 1242	< 260	< 70	< 150	< 180	< 250	< 180

* Medians of six collections made during Fall 1975

† The median value measured for dieldrin was 10 ng/m^2-day

Two types of samplers were used: an unoiled iced fallout sampler, and a high volume air sampler made of a glass fiber filter and five layers of polyurethane foam padding. The sampling interval was 24 hours at El Segundo, and 48 hours for the other stations.

Table 45 gives the concentrations of chlorinated hydrocarbons detected in the high volume air samples for three of the stations. The DDT and PCB values are considered indicative of good sampling efficiency as most of these compounds was detected on the front layers of the foam pad. The *p*-dichlorobenzene values are questionable because of high and variable values of *p*-dichlorobenzene in the process blanks. The other chlorinated benzene concentrations are also suspect because of high values in the blanks, and very low levels detected in the samples.

TABLE 45

CHLORINATED HYDROCARBONS (ng) MEASURED IN HIGH-VOLUME AIR SAMPLES COLLECTED OFF LOS ANGELES BASIN, 1976*

(Young *et al*., 1976)

	Filter (net)	Foam Pads (net)			Process Blanks	
		1st	3rd	5th	Filter	Foam
El Segundo (2/26-27):						
PDCB	< 62 †	1,600†	200†	240†	145	2,090
ODCB	<14 †	500	< 15	48	28	22
1,2,4-TCB	< 6 †	37	51	30	< 6	30
1,3,5-TCB	< 3 †	21	12	22	< 3	7
HCB	< 1 †	225	248	68	< 1	< 0.2
Total DDT	610	2,630	< 8	< 17	< 13	< 12
Aroclor 1254	390	4,220	73	6	< 22	22
Catalina Is. (4/6-8):						
PDCB	103	100†	150†	100†	428	660
ODCB	-	56	68	30	945	5
1,2,4-TCB	< 2 †	14	18	12	< 1.5	9
1,3,5-TCB	< 3	44	6	< 0.3	11	< 0.2
HCB	0.2†	35	27	22	0.2	0.8
Total DDT	4	260	10	18	4	8
Aroclor 1254	14	1,420	48	260	16	25
San Clemente (3/15-17):						
PDCB	38	250	850	70	80	350
ODCB	< 2.6†	< 2	< 6	< 1	< 2.6	< 2.6
1,2,4-TCB	< 1.0	5	15	1	< 1.0	18
1,3,5-TCB	< 0.4	< 1	< 1	< 1	< 0.4	1.3
HCB	< 0.2	55	60	54	< 0.2	4.4
Total DDT	18	620	2	13	< 1.8	7
Aroclor 1254	15 †	1,560	13	120	28	24

---

*Approximately 2000 m^3 sampled per 24 hour day

†Gross value

Consideration of this data leads Young to conclude that aerial fallout of chlorinated benzenes is much less likely than fallout of DDT and PCBs, because of the higher volatility of the former compounds.

The Environmental Research Laboratory at Duluth, Minnesota, has been monitoring chlorinated benzene content of fish taken from Lake Superior and Lake Huron. While detecting HCB for a number of years, they have recently observed trichlorobenzene as a result of improvements in analytical techniques (Veith, 1976). Figure 19 gives the GLC/MS spectrum for chlorinated benzenes found in trout taken from Lake Superior. Figure 20 presents data for burbot caught in Lake Huron. The mass number ranges were used to identify the following chlorobenzene isomers: trichlorobenzenes, 180 to 184; tetrachlorobenzenes, 214 to 218; pentachlorobenzene, 248 to 252; and hexachlorobenzene, 282 to 286.

Levels of HCB in trout were 70 ppb and levels in burbot were 10 ppb. The results are similar to data applicable to fish extracts taken from Lakes Ontario and Michigan, and the Detroit, Ohio and Hudson Rivers. Veith believes that the large amount of trichlorobenzene detected is due to its heavy use in askarels to reduce viscosity of the mixture.

Pentachlorobenzene has been detected in the living and non-living environments. In a two month survey of 212 samples of animal feed, fat and poultry products, Greve (1973) identified pentachlorobenzene as a limited contaminant of animal fat, eggs and meat products. Five samples of pork fat originating from the same farm contained pentachlorobenzene in excess of 0.02 ppm, and as high as 0.09 ppm (by electron capture/gas liquid chromatography). Fodder samples from the same farm contained 3.7 ppm pentachlorobenzene (QCB) and 45 ppm hexachlorobenzene. It was not established whether or not

FIGURE 19 CHLORINATED BENZENES AS FOUND IN LAKE SUPERIOR TROUT NEAR COPPERMINE POINT (Veith, 1976)

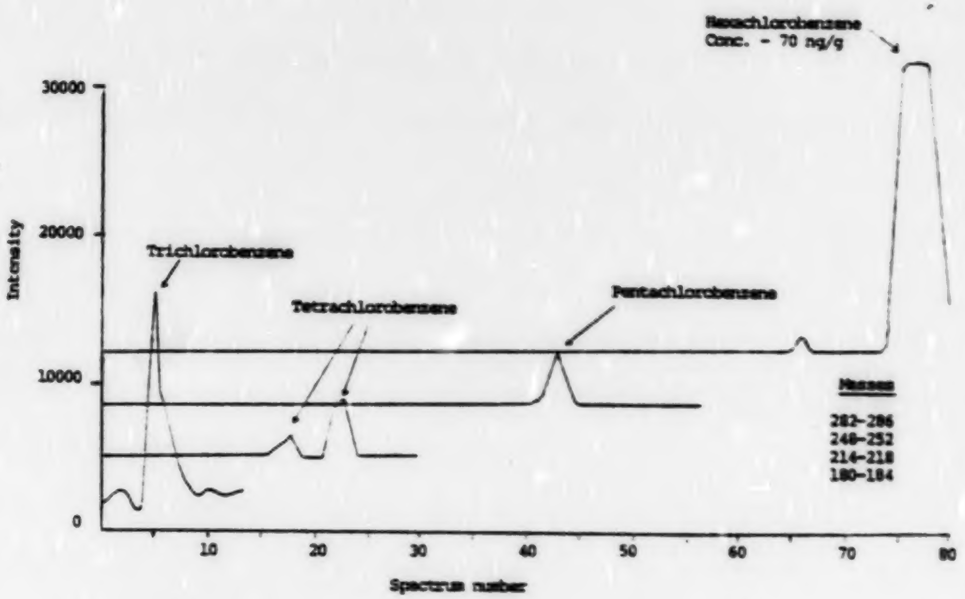
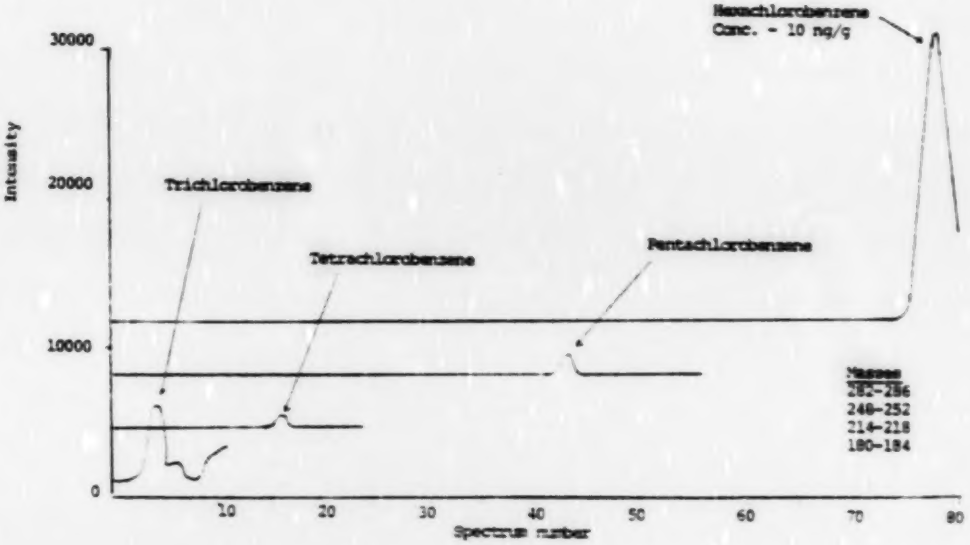


FIGURE 20 CHLORINATED BENZENES AS FOUND IN LAKE HURON BURBOT NEAR MACKINAC (Veith, 1976)



this same fodder had been fed to the pigs. The fodder contained spinach seed which had been treated with HCB.

Fifteen samples of the wheat and pollard pellets were analyzed. They contained in excess of 0.01 ppm of pentachlorobenzene with a high value of 0.15 ppm (electron capture GLC). Pentachlorobenzene content correlated with HCB content of the feed, supporting the belief that the pentachlorobenzene was a contaminant of the fungicide, HCB.

Both HCB and QCB have been detected in chicken fat (Stijve, 1971) where pentachlorobenzene was present in amounts between 7 to 15% of the HCB content

Beck and Hansen (1974) analyzed 22 soil samples from fields spread with technical grade pentachloronitrobenzene (PNCB) for a period of 11 years. Analysis of the samples by electron capture gas chromatography showed that for soils treated with PCNB up to 1970, there was an average accumulation of 0.37 mg of pentachlorobenzene per kilogram of soil. For samples treated for an additional two years, average accumulation of QCB was 0.32 mg/kg soil.

Ten samples of greenhouse soil analyzed for PCNB and HCB content were also found to contain pentachlorobenzene (DeVos et al., 1974). Data were developed by mass spectrometry after initial screening by electron capture/ liquid chromatography . Pentachlorobenzene and hexachlorobenzene were both detected in small amounts in the feces of beagle dogs fed PCNB for up to two years. The primary metabolite was pentachloroaniline (Kuchar et al., 1969).

All three dichlorobenzenes were detected in human blood samples collected in the New Orleans area (Dowty et al., 1975). None of the chlorinated benzenes were detected in a 400 liter sample of air nor in New Orleans drinking water, though many other organic compounds were confirmed. It was not clear how the dichlorobenzenes entered the human body, nor their point of origin.

As previously mentioned, Morita and Ohi (1975) detected p-dichlorobenzene in human adipose tissue and blood samples taken in the Tokyo Metropolitan Area. Average concentration in blood was 9.5 µg/ml, and in adipose tissue was 2.3 µg/ml. They also detected 1,2,4,5-tetrachlorobenzene and hexachlorobenzene in human adipose tissue at levels above 0.010 µg/g fat.

To summarize, many of the chlorinated benzenes appear to be widespread in the abiotic environment having been detected in rivers, lakes, municipal and industrial discharges, ground water, drinking water, air and soil. Monobromobenzene, dibromobenzene (isomer not specified) and bromochlorobenzene have also been detected in drinking water.

Several chlorinated benzenes have been detected in living organisms including fish, chickens, pigs, cattle and humans. Fish in Lakes Huron and Superior contained higher concentrations of hexachlorobenzene and trichlorobenzene isomers with smaller amounts of tetrachlorobenzene and pentachlorobenzene. Dichlorobenzenes have been detected in human blood samples taken in New Orleans and Tokyo, Japan, and p-dichlorobenzene, 1,2,4,5-tetrachlorobenzene and hexachlorobenzene have been found in human adipose tissue.

III. HEALTH AND ENVIRONMENTAL EFFECTS

A. ENVIRONMENTAL EFFECTS

1. Persistence

It is clear that there is now a greater awareness of the extent of environmental contamination by chlorinated benzenes. Certain chlorinated benzenes are extremely resistant to chemical, biological or photolytic degradation, and have been detected in wildlife and aquatic ecosystems. The persistence and distribution of hexachlorobenzene in the environment has received much attention. Improved analytical techniques and increased monitoring efforts are producing evidence of persistence of lower chlorinated benzenes, including penta-, tetra-, tri- and dichlorobenzenes. In this context, it is imperative to establish the extent of degradation of all of the chlorinated benzenes which are now being detected in the biosphere.

(a) Biological Degradation

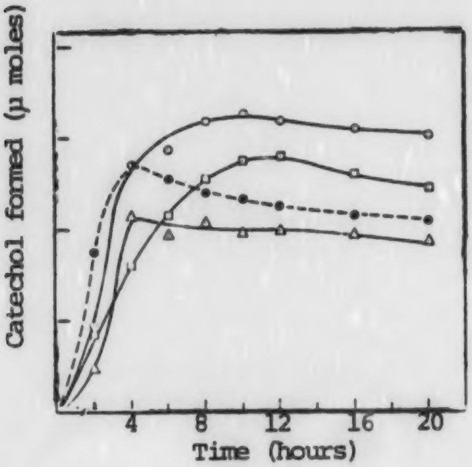
In general, halogenated benzenes may be broken down in the environment. The extent to which they do break down varies greatly, and depends on a number of factors including type of halogen, and number and position of halogens in the ring. The higher halogenated compounds are more resistant to biodegradation.

The oxidative degradation of the monohalogenated benzenes by *Pseudomonas putida* has been investigated by Gibson *et al*. (1968). Monochloro-, monobromo-, and monoiodobenzene were oxidized to the 3-halocatechol at approximately the same rate. The rate of oxidation of monofluorobenzene was half that of monochlorobenzene. Figure 21 shows the accumulation of halogenated catechols in cultures of *P. putida* initially grown on toluene for 15 hours and then grown on a halogenated benzene for up to 20 hours. *P. putida*

FIGURE 21

ACCUMULATION OF HALOGENATED CATECHOLS IN A CULTURE WITH *P. PUTIDA*

(Gibson *et al.*,1968)



Key

○-○ 3-Iodocatechol
□ □ 3-Bromocatechol
●-●-● 3-Chlorocatechol
▲ ▲ 3-Fluorocatechol

Reprinted with permission from Gibson, D.T., *et al.* Oxidative Degradation of Aromatic Hydrocarbons by Microorganisms. II. Metabolism of Halogenated Aromatic Hydrocarbons. Biochem., 7(11):3796, 1968. Copyright by American Chemical Society.

grows rapidly on toluene. The concentration of each halogenated benzene was corrected for the vapor pressure of the compound. Toluene served as the sole source of carbon and the halogenated benzenes were always added as an additional substrate for each of the oxidative systems. None of the halobenzenes served as a growth substrate when introduced into the medium by blowing air first through the incubation flask containing the monohalobenzene and then into the medium. It appears from this study that P. putida can only oxidize halogenated benzenes when they are already growing on an aromatic carbon source.

Lu and Metcalf (1975) reported values for the biodegradability index of monochlorobenzene ranging from 0.014 to 0.063 in organisms found in the model aquatic ecosystem described in Section 2 below. The biodegradability index (BI) is defined as the ratio of polar products of degradation to the nonpolar products. A low value of BI indicates that a compound resists biodegradation. For comparison, Lu and Metcalf reported a biodegradability index for DDT of 0.012 in mosquito fish compared to 0.014 for monochlorobenzene, and 0.015 for aldrin.

There is a report that Bacillus polymyxa utilizes monobromobenzene as the sole source of carbon (Shelat and Patel, 1973). B. polymyxa was isolated from sewage sludge and identified by the poured plate method using a mineral solution containing 0.5% w/v of monobromobenzene as the sole source of carbon. Ammonium nitrate was the nitrogen cource. After 72 hours incubation at 28°C, lobate translucent and fimbriate colonies were formed. These colonies were identical to B. polymyxa colonies grown on nutrient agar. The method of utilization was still to be determined.

The effects of biological action on the lower chlorinated benzenes in aqueous systems has been studied by Garrison and Hill (1972). Mono-, *o*-di- and *p*-dichlorobenzene volatilized completely from aerated mixed cultures of aerobic microorganisms in less than a day. 1,2,4-Trichlorobenzene persisted for nine days. No additional data were given.

There are other reports of the biological degradation of lower chlorinated benzenes. Midwest Research Institute (1974) reported that *p*-dichlorobenzene is degradable by biological organisms to 2,5-dichlorophenol, dichloroquinol and conjugates. No additional information was given, nor were references supplied. Gubser (1969) reported that *o*-dichlorobenzene is degraded by sewage sludge organisms. The degradation products were not given.

Using sewage microflora, Heukelekian and Rand (1955) showed a relationship between the biochemical oxygen demand (BOD) of a chemical and its structure. They found that introduction of certain chemical groupings into the molecule resulted in a lowered BOD. For example, introduction of chlorine atoms into an organic molecule was shown to decrease BOD. This decrease in BOD indicates a resistance to microbial attack. The BOD of benzene was reported as 1.20 g/g while that of monochlorobenzene was 0.03 g/g. Alexander and Lustigman (1966) also found that the presence of a chlorine atom on the benzene ring retarded the rate of biodegradation.

Levels of approximately 0.46 mg/l of 1,2,3-trichlorobenzene were detected in effluents from a sewage plant treating textile wastes in Gastonia, N.C. (Lewis, 1975). 1,2,3-Trichlorobenzene was present in the effluents prior to treatment. The wastes were aerated in a lagoon, clarified and then chlorinated. There was no evidence that the 1,2,3-TCB was formed as a result of chlorination. This report suggests that 1,2,3-trichlorobenzene may not be biodegradable.

TABLE 46

EFFECTS OF 1,2,4-TRICHLOROBENZENE ON BOD

Source of Organisms	BOD_{20} (% of theoretical value)	Reference
Microorganisms from industrial waste treatment plant	78	Hintz, 1962
"	100	Alexander, 1972
Mixture of microorganisms from 4 different textile treatment plants	50	Porter and Snider, 1974
Microorganisms from "typical" treatment plant	0 (2 days)	Haas *et al.*, 1974

Table 46 summarizes twenty day biochemical oxygen demand data (BOD_{20}) for 1,2,4-trichlorobenzene. The BOD_{20} values are given as a % of the theoretical value. Determination of BOD which measures oxygen uptake of the chemical is at best only an indirect indication of degradation. Results are difficult to interpret unless either no oxygen uptake or 100% uptake are found. The test does not give an indication of degradation products.

Haas *et al.* (1974) subjected 1,2,4-trichlorobenzene (50 ppm) to preconditioned treatment plant cultures. After 50 hours, there was only a slight decrease in concentration (cells + waters) of 1,2,4-trichlorobenzene, probably due to atmospheric loss. Approximately 40% of 1,2,4-TCB was absorbed by the organisms, though not biodegraded.

Other studies have reported various values for the BOD_{20} depending on the conditions and microorganisms used. Simmons *et al.* (1976) undertook a quantitative study of the biodegradation of 1,2,4-trichlorobenzene in order to clarify the extent and rate of degradation and the role of acclimatization. They used unacclimatized industrial wastewater microorganisms in their study. After 10 days, nearly all (99%) of the 1,2,4-trichlorobenzene (initial concentration 1.7 mg/l) as measured by gas chromatography/electron capture had disappeared from the experimental mixture. However, the BOD value after ten days indicated that 55% of theoretical value was removed. The 45% theoretical oxygen demand remaining was assumed to be due to incompletely oxidized metabolites of 1,2,4-TCB probably incorporated in the cell wall. Like Haas _et al_. (1974), Simmons _et al_. (1976) found no apparent degradation as measured by BOD in the first few days of monitoring. However, gas chromatography/electron capture analysis indicated a 14% reduction in 1,2,4-TCB concentration after only 24 hours, a 36% reduction at 72 hours and a 43% reduction at seven days.

At a higher concentration of 1,2,4-TCB (2.6 mg/l), the rate of degradation was apparently lower for the first few days. After seven days, the concentration of 1,2,4-TCB had decreased 28% by gas chromatography/electron capture analysis. However, after ten days all the trichlorobenzene had disappeared from the BOD bottles.

The formation rate of $^{14}CO_2$ through biodegradation of 1,2,4-TCB by activated sludge was also examined by Simmons _et al_. After 5 days, 13% TCB remained. There was 56% conversion to carbon dioxide, 23% conversion to polar metabolites and 7% volatization as TCB. The maximum rate of overall conversion of 1,2,4-TCB to CO_2 was 40 mg/g MLVS*/day. Approximately 80% of the trichlorobenzene was adsorbed on solids, accounting for the low volatility from the system. It seems clear that biodegradability of 1,2,4-trichlorobenzene depends on a number of factors including: (a) prior exposure of the TCB; (b) aeration rate; (c) residence time; and (d) volatility.

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*MLVS - mixed liquor volatile solids

In a series of laboratory experiments, Beck and Hansen (1974) investigated the half-life of penta- and hexachlorobenzene in the soil. Table 47 summarizes their data.

TABLE 47

RATES OF DEGRADATION OF PENTACHLOROBENZENE and HEXACHLOROBENZENE IN SOIL (Beck and Hansen, 1974)

Compound	Concentration (kg/ha)	Slope ($x10^{-4}$)	S.D.* of Slope ($x10^{-4}$)	Half-life (days)
Pentachlorobenzene	10	15.4913	3.7817	194
Pentachlorobenzene	10	8.735	1.6819	345
Hexachlorobenzene	10	3.1056	1.1586	969
Hexachlorobenzene	10	1.4412	0.4813	2089

*S.D. - standard deviation
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The slope was determined from the regression lines for the relationship between time and concentration of compound. Half-lives (RL_{50}) were calculated from the equation $RL_{50} = -\frac{\log 2}{\text{slope}}$. These results are not statistically significant. In order to show significant degradation of the two compounds, it is necessary to either alter the research protocol or extend the experiment. It does appear from this data, however, that QCB and HCB are very persistent in the soil.

An additional discussion of the biodegradability of chlorinated benzenes is found in Section 2 below.

(b) Chemical and Photolytic Degradation

Information relating to chemical and photolytic degradation is limited and concerns chlorinated benzenes only.

Dilling et al. (1976) studied the photodecomposition rates of a number of chlorinated hydrocarbons in a simulated atmosphere. Monochlorobenzene decomposed relatively slowly. In the presence of nitric oxide, MCB (10 ppm) underwent 43% reaction in 7.5 hours. This gives a half-life of 8.7 hours. The reactor was a water-jacketed Pyrex cylinder maintained at 27 ± 1°C and 35% relative humidity. Gas samples were analyzed by gas chromatography. Dilling et al. also studied the decomposition rates in combination with other organic compunds, but did not include chlorobenzene or any other halogenated benzene in this second phase of their study.

Both *o*- and *p*- dichlorobenzene are resistant to autoxidation by the peroxy radical (RO_2) in water, and by ozone (O_3) in air (Brown et al., 1975). The dichlorobenzenes are reactive to hydroxyl radicals (HO) in air with a half-life of approximately three days. Products of these reactions were not indicated. Hexachlorobenzene is also unreactive towards ozone and RO_2, but is moderately reactive toward HO in air, with a half-life of approximately two days. Pentachlorophenol is formed.

1,2,4-Trichlorobenzene is also susceptible to attack by the hydroxyl radical in air. The rate of degradation is not known, but is estimated to be of the order of one to several days (Simmons et al., 1976).

There is little information available relating to environmental hydrolysis of chlorinated benzenes which is of course limited by the insolubility of the compounds in water. There is a possibility that mono- and polyhydric phenols could be produced through hydrolysis. As previously mentioned, the halogenated benzenes are relatively stable to nucleophiles. The polyhalogenobenzenes are more easily attacked by nucleophiles such as OH^- because the electron attractive effect of the added halogens activates the ring. If environmental hydrolysis does occur, because of the insolubility of the compounds it must take place very slowly to form phenols or conjugates. It should be pointed out that higher chlorinated phenols are themselves highly toxic materials.

2. Bioaccumulation and Biomagnification

Lu and Metcalf (1975) studied the environmental fate and biodegradability of relatively volatile benzene derivatives in a model aquatic ecosystem. A three-liter flask containing daphnia, mosquito larvae, snails, green filamentous algae and mosquito fish was maintained at 80°F with 12 hour daylight exposure. Air and minerals were provided. Radiolabelled derivatives were added to the flask in concentrations of 0.01 to 0.1 ppm. After 24 hours, larvae, daphnia and fish were removed for radioassay, and after 48 hours, the experiment was terminated. The quantities of parent compound, metabolites and degradation products were radioassayed, and where possible identified.

Monochlorobenzene and hexachlorobenzene were found to be highly persistent compounds. Table 48 illustrates the extent to which the various species retained the halobenzenes. The mosquitos degraded approximately 65% of monochlorobenzene to form mainly the hydroxylated compounds, o- and p-chlorophenol and 4-chlorocatechol. These three compounds were also found in the water. o-Chlorophenol was identified in algae, and both chlorophenols in all other species. A number of degradation products were not identified.

TABLE 48

ECOLOGICAL MAGNIFICATION (EM)* OF MONOCHLOROBENZENE AND HEXACHLOROBENZENE IN VARIOUS AQUATIC SPECIES

(Lu and Metcalf, 1975)

SPECIES		CHEMICAL		
Common Name	Generic Name	MCB	HCB	PCP
Mosquito fish	*Gambusia affinis*	645	1166	296
Mosquito larvae	*Culex quinquifasciatus*	1292	2622	16
Snails	*Physa*	1313	2672	121
Daphnia	*Daphnia magna*	2789	1129	165
Algae	*Oedogonium cardiacum*	4185	3969	1.58

(cf. Ecological magnification of aldrin in mosquito fish = 1,312; EM of DDT in mosquito fish is 16,960.

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* The ecological magnification (or bioconcentration) is the ratio of the concentration of the chemical in an organism to the concentration in water.

Hexachlorobenzene was largely unchanged in the snail (84% of radioactivity), in daphnia (67%), in mosquito larvae (65%) and in fish (64%). The only identified degradation product was pentachlorophenol which was found in algae, mosquito larvae and water extracts. [Note: pentachlorophenol (PCP) was also studied in this investigation, see table above for EM values.] Pentachlorophenol is degraded by microorganisms to lower chlorinated phenols (Menzies, 1974).

This study also established a significant correlation between water solubility, partition coefficient and Hammett σ constant. Water solubility and partition coefficient apparently control the degree of bioaccumulation, while σ constant limits metabolism. The partition coefficient is defined as the ratio of the equilibrium concentration of the chemical between a non-polar and a polar solvent. In all the examples in Table 49, the solvents are n-octanol and water.

Laska et al. (1976) investigated the biomagnification of hexachlorobenzene in mosquito fish. Concentrations of hexachlorobenzene in mosquito fish ranged from 71.8 ppb at Garyville, to 379.8 ppb above Baton Rouge. The latter concentration represents a biomagnification of 172. Concentrations of HCB in crayfish were from 22.2 ppb at Romeville to 194.3 ppb at Darrow.

It is clear from an examination of Tables 48 and 49 and the literature references, that the chlorinated benzenes investigated are persistant chemicals which may be accumulating in the environment. Additional data are required to quantify the extent of any possible accumulation. No data were available relating to the brominated, fluorinated, or iodinated compounds.

3. Environmental Transport

The comparatively high volatility of the chlorinated benzenes suggests that they must rapidly vaporize and distribute through the atmosphere. Garrison and Hill (1972) showed that mono-, o-di-, p-di- and 1,2,4-trichlorobenzene volatilized from aerated distilled water in less than four hours. Concentrations were 300 mg/l, 100 mg/l, 300 g/l and 100 g/l respectively. The same concentrations of the four chlorinated benzenes volatilized from unaerated distilled water in less than three days. 1,2,4-Trichlorobenzene disappeared from unaerated water in less than two days. Once in the air, the

TABLE 49

MOLECULAR PROPERTIES AND BIOLOGICAL RESPONSE OF SEVERAL CHLORINATED BENZENES

Compound	Water Solubility ppm	Log Partition Coeffic.	Partition Coefficient	EM mosquito fish	BI mosquito fish	References
Monochlorobenzene	100	2.176	150	650	0.014	Lu and Metcalf, 1975
_o_-Dichlorobenzene	0.145g/1	3.38	2,399			Brown _et al._, 1975
_p_-Dichlorobenzene	0.008g/100g	3.39	2,455	-	-	Brown _et al._, 1975
_p_-Dichlorobenzene	insol.	3.38	2,399			Neely _et al._, 1974
Hexachlorobenzene	0.006	4.132	13,560*	1,166	0.377	Lu and Metcalf, 1975
Hexachlorobenzene	0.006	6.18	1,514,000*	-		Neely _et al._, 1974

*Note - the discrepancy between the two values of partition coefficient for hexachlorobenzene. The first value is experimentally derived, while the second value is calculated from the partition coefficient for _p_-dichlorobenzene by adding a substituent constant (0.7/Cl atom) for each chlorine atom substituted in the ring. In view of this discrepancy, it was decided not to calculate partition coefficients for other chlorinated benzenes using the substituent constant.

chlorinated benzenes are subject to OH attack. No degradation products were detected in the water.

Simmons et al. (1976) calculated that the rate constant for evaporation of 1,2,4-trichlorobenzene from water is 9.3 cc/hr. This corresponds to a half-life of 45 minutes in weter 10 cm deep measured at standard temperature and pressure.

Young et al. (1976) indicated that since chlorinated benzenes have a higher volatility than either DDT or PCBs, they are less likely to be carried from the atmosphere to land or water as dry particulate fallout. Additional data relating to aerial fallout of chlorinated benzenes off southern California is found in Section IIF.

There is also a possibility that 1,2,4-trichlorobenzene will be transported through water. Simmons et al. (1976) indicated that 75% of 1,2,4-TCB which remains in water (i.e. which is neither biodegraded nor volatilized) is associated with solids in the waste sludge. Haas et al. (1974) reported that approximately 40% of 1,2,4-TCB is absorbed into the cell wall of sludge microorganisms. The extent to which 1,2,4-TCB is transported through flowing water attached to particulate matter has not yet been investigated.

There has been at least one study of the distribution of hexachlorobenzene and hexachlorobutadiene in water, soil and microorganisms along the lower Mississippi River in Louisiana (Laska et al., 1976). Samples were taken at five mile intervals between Baton Rouge and New Orleans and south to Port Sulphur, a distance greater than 100 miles. Water samples (1 liter) were collected near the river's edge at depths of approximately 15 cm. Soil samples from beneath the water surface were taken from the levee at the same location. Mud samples were obtained from the adjacent drainage ditch running parallel to the levee. Fish and aquatic invertebrates were sampled where located.

Hexachlorobenzene and/or hexachlorobutadiene were found in every water collection between Baton Rouge and New Orleans. A concentration of HCB (2.2 ppb) was recorded above Baton Rouge, downstream from a heavily industrialized area. HCB is formed as a by-product by chemical plants in the vicinity of Plaquemine and Darrow, where a water sample contained 90.3 ppb HCB (electron capture GLC). Hexachlorobenzene carried in suspension by the river accumulated in soil from the levee and the drainage ditch in concentrations to a high of 874.4 ppb at Darrow. Runoff from the slopes of the levee accounted for accumulation of HCB in drainage ditches. HCB was also detected in soil samples at three sites well removed from the transect along the Mississippi River.

More information is clearly required to determine the factors involved in environmental transport of chlorinated benzenes. The persistence and accumulation of chlorinated benzenes in the atmosphere must also be further studied.

B. BIOLOGICAL EFFECTS

1. Toxicity and Clinical Studies in Man

(a) Poisoning Incidents and Case Histories

Most of the poisoning incidents reported in the literature resulted from inhalation of chlorinated benzenes. Accidental inhalation can occur either in the home or at work. There are several cases, however, when a chlorinated benzene was either accidentally or deliberately ingested (see Table 50).

Monochlorobenzene (MCB)

Atmospheric exposure to monochlorobenzene causes headaches, irritation of eyes and upper respiratory tract, numbness, inhibition and eventual loss of consciousness (Girard *et al*., 1969; Smirnova and Granik, 1970). A two year old male survived ingestion of 5 to 10 ccs of MCB. When hospitalized, he was unconscious, cyanotic and twitching in the head and neck regions (Reich, 1934). There was no long term follow-up of this patient.

Chlorobenzene causes a burning sensation or irritation in contact with skin (Dow Chemical, 1977b). In contrast to benzene and hexachlorocyclohexane, the irritation appears to last for a long time, indicating an absence of appreciable analgesic or local anesthetic effects. Severe irritation is characterized by erythema, hyperemia and wheal formation (Von Oettingen, 1955).

Dichlorobenzenes

One case of sensitization to *o*-dichlorobenzene was reported for a man who regularly handled window sashes dipped in the compound (Downing, 1939). When applied to the skin, there was a burning sensation after 15 minutes and for the duration of exposure. The site of application showed a reddish hue which increased up to 24 hours later, when blisters formed. A brown pigmentation formed later and persisted for three months. The man was forced to seek alternative employment.

Girard *et al.* (1969) reported three cases of leukemia resulting from chronic exposure to *o*-dichlorobenzene (ODCB). One man hospitalized for chronic lymphoid leukemia worked with a solvent containing 80% ODCB and 15% *p*-dichlorobenzene (PDCB) for 10 years. A girl hospitalized with acute myeloblastic leukemia died 10 months later of peripheral leukoblastosis. She reportedly had a neurotic compulsion to remove dirt and grease stains from her clothes, which she did repeatedly with a product containing 37% ODCB (no benzene or toluene). Another man exposed to a glue containing 2% *o*-dichlorobenzene, methyl ethyl ketone and cyclohexane for a period of 29 years died of chronic lymphoid leukemia. No further details of these incidents were given.

In cases where moderate exposure to *p*-dichlorobenzene were documented, patients complained of severe headaches, profuse rhinitis and periorbital swelling for approximately 24 hours after exposure (Cotter, 1953; Campbell and Davidson, 1970). Anorexia, nausea, vomiting, weight loss and yellow atrophy of the liver were reported for high exposure concentrations (Petit and Champeix, 1948; Cotter, 1953; Hallowell, 1959).

Wallgren (1953) reported loss of weight, exhaustion, decrease of appetite and blood dyscrasias in 27 men who manufactured *p*-dichlorobenzene for 1 to 7 months. Cotter (1953) described the case of a woman who demonstrated products containing PDCB and who complained of tiredness, nausea, headache and vomiting. Clinical studies showed that she had subacute yellow atrophy and cirrhosis of the liver.

Heavy use of *p*-dichlorobenzene as either a moth-repellent or a deodorizer has apparently resulted in weakness, nausea, blood vomiting and jaundice (Perrin, 1941; Cotter, 1953; Weller and Crellin, 1953). One man and his wife died within months of each other of acute yellow atrophy of the liver (confirmed by autopsy). Their house was apparently saturated with PDCB moth ball vapor for a period of at least three to four months (Cotter, 1953).

There are at least two reports of deliberate ingestion of p-dichlorobenzene. One woman who developed a pica for PDCB during the first trimester of her pregnancy complained of general tiredness, mild anorexia, dizziness and edema of the ankles. She was hospitalized with hemolytic anemia and delivered a health child several months later (Campbell and Davidson, 1970). Another woman who ingested 4 to 5 PDCB pellets (size not indicated) daily for 2 1/2 years complained about increased patchy pigmentation. Unsteadiness and tremors occurred when she stopped taking the pellets, but these symptoms were thought to be due to psychological rather than physiological withdrawal (Frank and Cohen, 1961).

Other Chlorinated Benzenes

There is a report of severe aplastic anemia in a man who regularly soaked his clothes in trichlorobenzene to remove grease (Girard *et al.*, 1969).

In 1955, there was an outbreak of cutaneous porphyria in southeastern Turkey which was traced to consumption of wheat treated with hexachlorobenzene. Over 5000 cases were reported, mostly in children. Intake of HCB was as high as 200 mg/day for several months before the epidemic was recognized. Symptoms disappeared when contaminated wheat was no longer eaten (Ockner and Schmid, 1961).

2. Effects on Nonhuman Mammals

(a) Absorption and Excretion

The absorption and excretion of halogenated benzene compounds takes place by the method of simple diffusion. Halogenated benzenes may be absorbed from

TABLE 50 HUMAN EXPOSURE TO CHLORINATED BENZENES - CASE REPORTS

Subject	Exposure	Symptoms	Clinical Report	Follow-up Studies	Reference
70 year old female	1958-1964 to a glue containing 07% MCB (no benzene or higher homologues)	Headaches, irritation of eyes and upper respiratory tract	Medullar aplasia	1966- "satisfactory" 1967- "mediocre"	Girard et al., 1969
2 year old male	Swallowed MCB, 5-10 cc	Unconscious, no reaction to skin stimuli, muscle spasms, cyanotic	MCB intoxication	Odor of MCB present in urine and air exhaled 5-6 days later. General health appeared undisturbed	Reich, 1934
3 adults	Occupational exposure to MCB	Numbness, inhibition, loss of consciousness, hyperemia of conjunctivae, scelera, pharynx	MCB intoxication	Follow-up studies were performed, data not clear on results	Smirnova and Granik, 1970
Sewage workers	ODCB effluents from dry-cleaning establishment above sewer	Eye and upper respiratory tract irritation, vomiting	ODCB intoxication	Not indicated	Dupont, 1938
47 year old male	ODCB in dipping solution for window sashes, occupational	Water blisters on face, hands, arms	Eczematoid dermatitis due to ODCB	Not indicated	Downing, 1939
40 year old male	1940-1950 occupational exposure to solvent - 80% ODCB, 15%-PDCB	Weakness, fatigue	Chronic lymphoid leukemia	Treatment on-going	Girard et al., 1969
18 year old female	Dry-cleaning and dyeing shop ODCB	Pallor, tiredness, headaches, vomiting, violent gastric pains	Severe hemolytic anemia 1.5 x 10^6 erythrocytes	10 months later, erythrocytes "excellent" but leucocyte equilibrium showed tendency to neutropenia	Gadrat et al., 1962
53 year old male	1932-1961, glue containing 2% ODCB, methyl ethyl ketone & cyclohexane, (no benzene or homologues)	Weakness, fatigue	Chronic lymphoid leukemia, peripheral and abdominal adenopathy, splenomegalia	Died 1968	Girard et al., 1969
15 year old female	Cleaned clothes with products containing 37% ODCB, (no benzene or toluene)	Initially hospitalized with retroclavicular adenopathy	Acute myeloblastic leukemia	Died 10 months later of 100% peripheral leukoblastosis	Girard et al., 1969
36 year old female	PDCB moth killer in house	Periorbital swelling, intense headaches, profuse rhinitis	Exposure to PDCB	Symptoms subsided within 24 hours	Cotter, 1953
21 year old pregnant female	Pica for PDCB toilet blocks, first trimester	General tiredness, mild anorexia, dizziness, edema of ankles	Hemolytic anemia	Healthy child delivered several months later	Campbell and Davidson, 1970
34 year old female	Demonstrating PDCB containing products	Tiredness, nausea, headache, vomiting	Subacute yellow atrophy and cirrhosis of the liver	Not indicated	Cotter, 1953

TABLE 50 (continued)

Subject	Exposure	Symptoms	Clinical Report	Follow-up Studies	Reference
19 year old female	Preparation of PDCB for 18 months	Asthenia, dizziness, weight loss	Slight anemia, reactional hyperleucocytosis	Not indicated	Petit and Champeix, 1948
20 year old male (+ 7 workmates)	PDCB manufacture 1 to 7 months exposure	Loss of weight, exhaustion, decrease of appetite	Methemoglobinemia and other blood pathologies	All workers transferred to other working environment	Wallgren, 1953
19 year old female (black)	4 to 5 PDCB pellets ingested daily for 2 1/2 years	Increased patchy pigmentation	Due to PDCB ingestion. Unsteadiness and tremors on ceasing consumption thought psychological not physiological	Pigment returned to normal	Frank and Cohen, 1961
60 year old male	Heavy PDCB moth ball vapor in house for 3 to 4 months	Weight loss, loose bowels, tarry stools, numbness, clumsiness	Acute yellow atrophy of the liver (confirmed by autopsy)	Developed ascites and died	Cotter, 1953
Wife of male above	As above	Weight and strength loss, abdominal swelling, jaundice.	Acute yellow atrophy of the liver (confirmed by autopsy), splenomegaly	Died 1 year after initial exposure	Cotter, 1953
52 year old male	PDCB exposure in fur storage plant	Weakness, nausea, blood vomiting, jaundice.	Subacute yellow atrophy of the liver	4 years later reported "in good health "	Cotter, 1953
62 year old male	PDCB in bathroom	Asthenia, dizziness	Light hyperchronic anemia, after 1 month increase in anemia, hypogranulocytosis	General hematological improvement but increase in hypogranulocytosis at 6 months	Perrin, 1941
53 year old female	12 to 15 year exposure to PDCB moth balls in house	Cough, progressive dyspnea, fatigue, mucoid sputum	Pulmonary granulomatosis? focal necrosis of liver	Not indicated	Weller and Crellin, 1953
3 year old male	Played with PDCB, crystals	Cough, listlessness, black urine	Acute hemolytic anemia	Complete recovery	Hallowell, 1959
68 year old male	Cleaned with basins of trichlorobenzene (manner not spec.)	Weakness, tiredness	Acute hemolytic anemia	Complete recovery	Girard *et al.*, 1969
60 year old male	1930 to 1960 shipping mono, o-di- and trichlorobenzene	Weakness, tiredness	Anemia, 3×10^6 erythrocytes	Not indicated	Girard *et al.*, 1969
Male worker	Exposure to MCB, leaking pump sprayed into atmosphere	General discomfort, massive hemoptysis several hours later	Poisoning due to MCB	Not indicated	Ehrlicher, 1968
Epidemic	Exposure to agricultural chemical HCB. Seeds were eaten by a population	Porphyria cutanea tardia, hepatomegaly, hydroa aestivale	Porphyria	———	Ockner and Schmid, 1961

the gastrointestinal tract, the lungs, and through the skin. Higher halogenated benzenes, in general, are more poorly absorbed from the gastrointestinal tract than the lower homologues. Most of the halobenzenes are relatively insoluble in water, and possess varying degrees of high lipid solubility. These lipid soluble compounds cross most of the barrier membranes in the animal including the gastrointestinal epithelium, the hepatic parenchyma, placental membranes, renal tubules and the skin.

When halogenated benzenes enter the body, mono-, o- and m-dihalogenated, 1,2,3- and 1,2,4-trihalogenated, and the 1,2,3,4-tetrahalogenated benzenes are metabolized to a greater extent than the p-di- and 1,3,5-tri-, 1,2,4,5- and 1,2,3,5-tetrahalogenated, penta- and hexahalogenated benzenes. Those compounds which escape biotransformation may be excreted in part unchanged in the urine, feces or expired air. Alternatively, they may change spontaneously after an initial oxidative reaction. This 'spontaneous reaction', for the most part with glutathione (later shown to be enzymatic), gives rise to mercapturic acids in the urine (Williams 1959; Boyland and Chasseaud, 1969).

Carbon tetrachloride, chloroform and trichloroethylene once considered relatively inert, have been reinvestigated (Daniel, 1963; Paul and Rubinstein, 1963). With the use of modern techniques, it has been shown that they are metabolized to a minor extent. This minor extent of metabolism is a very important aspect of both acute and chronic toxicity (National Cancer Institute, 1976a, 1976b). Similarly, halogenated benzenes which are not extensively metabolized could be hazardous (if they form an arene oxide intermediate) since an overall effect of metabolism is to make compounds more polar and less lipid soluble and/or more water soluble so that they can be readily excreted (Williams, 1959). Lipid soluble halogenated benzenes, which undergo biotransformation to a minor extent, not only tend to accumulate in the body and reach toxic levels, but may recirculate for long periods of time. Toxic intermediates produced through metabolism may cause repeated insults on a tissue, increasing the chance for cellular damage. The tendency toward cumulative effects is greater as the number of halogens per benzene ring increases. However, the number of halogens is not the only variable. The presence or absence of vicinal positions, the vapor pressure of the compound, its lipid solubility, the halogen substituent and the extent of metabolism are all variables.

Monohalogenated Benzenes

Halogenated benzenes are eliminated partly in urine, bile, feces, and expired air. The biliary route of elimination depends upon the species and the molecular weight of the compound. Air expired from the lungs is an important route of excretion of the more volatile halogenated benzenes such as monofluoro- and monochlorobenzene.

Parke and Williams (1950) and Azouz *et al*. (1952) noted in studies on rabbits that monofluorobenzene (b.p. 85°, v.p. 96.6 mm at 30°C) behaves more like benzene than the other monohalogenated compounds. As can be seen in Table 51, 44% of fluorobenzene (0.5 mg/kg body weight) is excreted via the lungs. If the dose were doubled, 64% of fluorobenzene would be eliminated unchanged by this route. Monochlorobenzene has a higher boiling point (132°C) and a lower vapor pressure (v.p. 15.5 mm at 30°C) than fluorobenzene. Hence, only 27% of the total dose of MCB (0.5 mg/kg body weight) is excreted via the lungs. Only a small amount of the higher boiling monobromo- and iodobenzene are exhaled unchanged. About 6% of an oral dose of bromobenzene (v.p. 5.7 mm at 30°C) is respired unchanged (see Table 51). The overall elimination of

TABLE 51

A COMPARISON OF MAJOR METABOLITES OF BENZENE AND MONOHALOGENATED BENZENES IN RABBITS AFTER AN ORAL DOSE (0.5 mg/kg body weight)

(Azouz *et al.*, 1952)

Compound	Glucuronides (% of original dose)	Ethereal Sulfate (% of original dose)	Mercapturic Acid (% of original dose)	Unchanged* (% of original dose)	Vapor Pressure† (mm Hg)	Total (% of original dose)
Benzene	11	25	1	39	117.5 (78)	76
Fluorobenzene	10	21	1.6	44	96.6 (96)	77
Chlorobenzene	25	27	20.0	27	15.5 (112.5)	99
Bromobenzene	40	37	21.0	6	5.7 (157)	104
Iodobenzene	31	40	23.0	3	1.5 (204)	87

* Pulmonary excretion.

† Vapor pressure at 30°C from Young, 1910.
Numbers in parentheses represent molecular weight.

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unchanged monohalogenated benzenes usually takes 30 to 40 hours in the rabbit (Parke and Williams, 1950; Azouz et al., 1952; Williams, 1959).

Some 30% or more of the monohalogenated benzenes are oxidized in vivo and may be excreted via kidneys as ethereal sulfates, mercapturic acids and glucuronides. The oxidized forms include monohalogenated phenols and catechols. The ethereal sulfate and glucuronic acid conjugates show considerable variation quantitatively in the rabbit. Relative amounts produced depend on the halogen substituent. Mercapturic acids (conjugates of glutathione) are also excreted via the kidney. For rabbits, about 25% of a dose (0.5 mg/kg body weight) of chloro-, bromo- and iodobenzene is excreted as mercapturic acids (Parke and Williams, 1950: Azouz et al., 1952).

In the rabbit, monofluorobenzene is excreted as conjugates of glucuronic acid (10% of original dose), ethereal sulfate (21%) and glutathione (1.6%) (Parke and Williams, 1950; Azouz et al., 1952). The glutathione conjugates, which appear in the urine mainly as mercapturic acids, are small when compared to equimolar doses of other monohalogenated benzenes. They resemble those derived from equimolar doses of benzene. Glutathione conjugates of chloro-, bromo- and iodobenzene are 20%, 21% and 23% of the total dose respectively. For MCB, glucuronic acid conjugates are 25% and ethereal sulfates are 27%. Conjugated glucuronic acid excretion is 40% of original dose for monobromobenzene, and 31% for monoiodobenzene, while sulfate excretion is 37% for monobromobenzene and 40% for iodobenzene (see Table 51).

Dichlorobenzenes

The dichlorobenzenes may be absorbed through the gastrointestinal tract, intact skin and lungs. After oral administration (0.5 mg/kg body weight) to rabbits, all dichlorobenzenes are slowly metabolized by oxidation, mainly to dichlorophenols. The phenols and their conjugation products are excreted in five to six days. The peak excretion occurs on the first day for o- and m- isomers, and on the second day for p-dichlorobenzene. The major phenolic metabolites of the dichlorobenzenes are shown below:

Isomer	Major Phenolic Product	% of total dose
o-Dichlorobenzene	3,4-Dichlorophenol	30%
m-Dichlorobenzene	2,4-Dichlorophenol	24%
p-Dichlorobenzene	2,5-Dichlorophenol	35%

About 3 to 11% of the o- and m- isomers are excreted as dichlorocatechols, though p-dichlorobenzene does not seem to form this metabolite. The o- and m- isomers form mercapturic acids (5 to 10% of total), but p-dichlorobenzene does not (Williams, 1959). The orientation of mercapturic acid is the same as for the major phenolic product for each isomer. In the case of o-dichlorobenzene, there are two monophenolic metabolites: 3,4- and 2,3-dichlorophenol. These metabolites do not reach their peak excretion at the same time; the 3,4-isomer peaks on the first day, and the 2,5-isomer on the second day. The phenolic metabolites are excreted conjugated with glucuronic and sulfuric acids (Azouz *et al*., 1952; Azouz *et al*., 1955; Parke and Williams, 1955).

Higher Chlorinated Benzenes

As the number of halogens on the benzene ring increases, mercapturic acid and catechol formation decreases. The tri-, tetra- and pentahalogenated benzenes are metabolized mainly to monohydric phenols, as is shown for polychlor inated benzene in Table 52 (Williams, 1959). The polyhalogenated compounds are slowly absorbed from the gastrointestinal tract, a fact which has made

TABLE 52

THE QUANTITATIVE ASPECTS OF THE METABOLISM OF HALOGENATED BENZENES IN RABBITS[*]

(oral doses of 0.5 g/kg body weight)
(Williams, 1959)

Compound	Time of excretion Days [§]	% of dose excreted as				Eliminated unchanged in expired air or feces
		Mercapturic Acid	Monophenols [†]	Catechols [†]	Total O-conjugates [‡]	
Benzene	1-2	1	25	2.5(5)	36	39 in air
Monofluorobenzene	1-2	1-2	+	12	31	44 in air
Monochlorobenzene	1-2	25	2-3	27	47	27 in air
Monobromobenzene	1-2	25	2-3	28	58	6 in air
Monoiodobenzene	1-2	25	2-3	21	53	3 in air
1,2-Dichlorobenzene	5	5	40	4	69	-
1,3-Dichlorobenzene	5	11	25	3	27	-
1,4-Dichlorobenzene	5	0	35	0 (6) [¶]	63	-
1,2,3-Trichlorobenzene	5	0.3	78	tr.	62	0 in feces
1,2,4-Trichlorobenzene	5	0.4	42	tr.	38	0 "
1,3,5-Trichlorobenzene	8	0	9	0	23	10(51) [#] "
1,2,3,4-Tetrachlorobenzene	6	0	43	tr.	34	5(10) [#] "
1,2,3,5-Tetrachlorobenzene	6	0	5	0	8	14(23) [#] "
1,2,4,5-Tetrachlorobenzene	6	0	2	0	5	16(48) [#] "
Pentachlorobenzene	6	0	1	0	9	5(50) [#] "
Hexachlorobenzene	6	0	0	0	0	6(77) [#]

[*] The figures in this table were obtained in the author's laboratory and are intended to give a rough indication of the various routes of metabolism of the halogenated benzenes.

[†] In some cases these figures give the amounts isolated.

[‡] Conjugated glucuronic acid + ethereal sulfate.

[§] The excretion of metabolites had not ceased after this time, but were being produced at a low rate.

[¶] These figures are for quinol.

[#] The figures in brackets are the percentages of the dose of hexa-, penta- and tetrachlorobenzenes which were found unchanged in the tissues six days after the dose.

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accounting for the total metabolites difficult. 1,4-Dihalogenated, 1,3,5-trihalogenated, tetra- and pentahalogenated benzenes probably do not undergo mercapturic acid formation in rabbits (Azouz _et_ _al_., 1952; Azouz _et_ _al_., 1955; Parke and Williams, 1955).

The three isomers of trichlorobenzene are absorbed from the gastrointestinal tract, intact skin and lungs. In rabbits, these compounds are metabolized in varying degrees to phenols (see Table 52). The 1,2,3- isomer is metabolized to a greater extent (78% of original dose) than either the 1,2,4- isomer (42%) or the 1,3,5- isomer (9%). All are excreted in about five days. Very small amounts of mercapturic acids are formed, and their spatial orientation is the same as the phenolic metabolites (Azouz _et_ _al_., 1952; Azouz _et_ _al_., 1955; Parke and Williams, 1955). The 2,4,5-trichlorophenol was shown to be partially dechlorinated to the extent of about 1%, yielding _p_-chlorophenol (Kohli _et_ _al_., 1976a).

Tetrachlorobenzene is absorbed through the gastrointestinal tract at a rate considerably lower than the mono- or dihalogenated benzenes (see Tables 52 to 54). The three isomers differ in their ability to undergo metabolism in rabbits. The 1,2,3,4- isomer is mainly converted to 2,3,4,5-tetrachlorophenol. The 1,2,3,5- and 1,2,4,5- isomers are highly resistant to oxidation. Some of the tetrachlorobenzenes are also partially dechlorinated (Kohli _et_ _al_., 1976a). The trichlorobenzenes and other dehalogenated benzenes which result from dechlorination may have formed in the gastrointestinal tract by the action of bacterial enzymes (Kohli _et_ _al_., 1976a).

In the rabbit, some pentachlorobenzene is converted to pentachlorophenol which has been shown to be highly toxic in a number of studies (Kohli _et_ _al_., 1976a). It usually takes about six days to eliminate the tetra- and penta-

TABLE 53

METABOLISM OF 1,3,5-TRI-, PENTA- AND HEXACHLOROBENZENE IN RABBITS
(Parke and Williams, 1960)

			Doses were given orally unless otherwise indicated							Total accounted for§ (%)
			% of Original Dose							
			Urine							
Compound	Dose (g/kg)	Time after dosing (days)	Tri- or penta-chloro-phenol	Other phenols	Feces	Gut contents	Pelt	Depot fat	Rest of body	
Trichlorobenzene	0.5	8	3	1	13	23*	5	5	22	85
	0.5	9	10	4	1.5	18	5	4.5	20	74
Penta-chlorobenzene	0.5	3	0.2	1	5	45	1	15	6	82
	0.5	4	0.2	1	5	31	5	9	5.5	78
	0.5†	10	0.7	1	1.5	0.5	47‡	22‡	10	85
Hexa-chlorobenzene	0.4	5	0	0	6	78	1	1	1	84
	0.4	5	0	0	6	73	1	1	2	83
	0.1	5	0	0	0.3	0.2	75	1	1	76

* 4% as monochlorobenzene
† Injected subcutaneously
‡ Located mainly at site of action
§ Small amounts were detected in the expired air
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TABLE 54

SUMMARY OF METABOLISM OF HIGHER CHLORINATED BENZENE ISOMERS IN RABBITS
(Kohli *et al.*, 1976a)

Compound Administered*	Metabolite	% Yield
1,2,4-Trichlorobenzene	2,4,5-Trichlorophenol	5
	2,3,5-Trichlorophenol	6
1,2,3-Trichlorobenzene	3,4,5-Trichlorophenyl acetate	2
	2,3,4-Trichlorophenol	11
	2,3,6-Trichlorophenol	1
1,3,5-Trichlorobenzene	2,3,5-Trichlorophenol	1.5
	2,4,6-Trichlorophenol	3.0
1,2,3,4-Tetrachlorobenzene	2,3,4,5-Tetrachlorophenol	20
	2,3,4,6-Tetrachlorophenol	2
1,2,3,5-Tetrachlorobenzene	2,3,4,5-Tetrachlorophenol	3
	2,3,5,6-Tetrachlorophenol	2
	2,3,4,6-Tetrachlorophenol	1.5
1,2,4,5-Tetrachlorobenzene	2,3,5,6-Tetrachlorophenol	2
Pentachlorobenzene	2,3,4,5-Tetrachlorophenol	1
	Pentachlorophenol	1
Hexachlorobenzene	————	—

* Dose was 300 mg in vegetable oil given to 4 to 5 kg rabbits by intraperitoneal injection.
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chlorobenzenes (see Table 52). The reasons for this delay may be enterohepatic circulation and/or high lipid solublity as is suggested from the results of Sipes et al. (1974).

The hexahalogenated benzenes in general are slowly absorbed from the gastrointestinal tract or intact skin. Hexachlorobenzene has been studied in greatest detail, while there are only a few scattered reports on other hexahalogen compounds. Hexachlorobenzene when administered orally to rabbits was not readily absorbed. After five days, about 85% of a dose (0.4 g/kg body weight) was recovered unchanged in the gastrointestinal tract and the feces (see Table 53)(Parke and Williams, 1960). Once absorbed, hexachlorobenzene is metabolized in trace amounts to pentachlorophenol (Lui and Sweeney, 1975). 1,2,4,5-Tetrachlorobenzene was also detected in the intestinal contents. Bacterial flora in the gastrointestinal tract may have contributed to these dehalogenations (Kohli et al., 1976a). Traces of dehalogenated compound were also found in the expired air for tests on monkeys (Yang et al., 1975).

Monobromobenzene

It has been shown in studies on rats that drug conjugates having a molecular weight greater than 300 are often excreted in the bile. Sipes et al. (1974) found conjugates of glutathione in the bile of rats and studied the effects of stimulation and inhibition of drug metabolism. They reported that after bromobenzene administation an increase in bile flow occurs following prior stimulation with phenobarbital, and a decrease following prior inhibition with 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride (SKF-525A) (see Table 55). It is apparent that in the rat, the biliary route represents a major means of excretion of metabolites of bromobenzene, and possibly of other halogenated benzenes. In the rat, 56% of the total dose was excreted

TABLE 55

EFFECTS OF PRETREATMENT OF RATS WITH PHENOBARBITAL (80 mg/kg, intraperitoneally (i.p.) for 3 days) AND SKF-525A (75 mg/kg, i.p. 2 hr before) ON THE BILE EXCRETION OF BROMOBENZENE METABOLITES AND ON BILE FLOW
(Sipes et al., 1974)

	Pretreatment					
	None		Phenobarbital		SKF-525A	
Time After Bromobenzene (min)	Bromobenzene metabolites (µmoles)	Volume of bile (ml)	Bromobenzene metabolites (µmoles)	Volume of bile (ml)	Bromobenzene metabolites (µmoles)	Volume of bile (ml)
0-30	2.9 ±0.38	0.59 ±0.04	9.1 ± 1.1 †	1.00 ±0.06 †	0.8 ±0.10 †	0.39 ±0.02 ‡
30-60	4.6 ±0.51	0.55 ±0.07	4.7 ± 0.56	0.80 ±0.04 ‡	3.4 ±0.30 ‡	0.42 ±0.03
60-90	2.9 ±0.43	0.55 ±0.06	2.1 ± 0.19	0.70 ±0.05	2.8 ±0.42	0.45 ±0.04
90-120	2.1 ±0.14	0.47 ±0.03	1.4 ± 0.08 †	0.60 ±0.04	2.1 ±0.37	0.42 ±0.03
120-150	1.3 ±0.12	0.42 ±0.04	0.67± 0.23 †	0.58 ±0.04	1.6 ±0.28	0.40 ±0.04
150-180	0.8 ±0.05	0.45 ±0.03	0.76± 0.08	0.58 ±0.06	1.0 ±0.15	0.46 ±0.07

* ^{14}C-bromobenzene was administered intravenously at a dose of 20 mg/kg (130 µmoles/kg body weight, sp. act., 2 µCi/µmole).

Each value is the mean of five to six rats ±S.E.

† $p < 0.01$ compared to control rats.

‡ $p < 0.05$ compared to control rats.

SKF-525A is 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride.

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in the bile. These biliary metabolites appear to be conjugates derived from the alkylation of glutathione by the highly reactive arene oxides or epoxides (Sipes et al., 1974). A correlation exists between the ability to form such arene oxide intermediates and hepatic cytotoxicity (Mitchell et al., 1971).

Reid et al. (1971b) and Zampaglione et al. (1973) indicated that 80% of a dose of monobromobenzene (oral administration 750 mg/kg body weight) may be recovered after 24 hours in the urine of rats as monophenols, catechols, conjugates of glucuronic acid, sulfate and glutathione. Sipes et al. (1974) found 56% of an intravenously injected dose of monobromobenzene (20 mg/kg body weight) in the bile after three hours. Hence, they suggested that the majority of the dose excreted in the bile must be reabsorbed from the intestine and later excreted via the kidney.

Table 56 shows the concentration of bromobenzene in the tissues of the rat after an oral dose of 750 mg/kg body weight. These tissue distribution studies revealed high concentrations in tissue when compared to plasma. Especially noteworthy was the higher concentration in adipose tissue. After reducing the dose to 250 mg/kg, the decline in most tissue concentrations was shown approximately to parallel that in the plasma. Also in these studies, adipose tissue had a somewhat longer half-life (Reid et al., 1971b).

Stimulators and inhibitors of drug metabolism may determine the extent of metabolism, which in turn determines the toxicity and distribution of the bromobenzene (Reid et al., 1971b; Zampaglione et al., 1973). Table 57 shows the effects of prior administration of phenobarbital (stimulator) and 3-methylcholanthrene (inhibitor) on the metabolism of bromobenzene in a study on rats. These findings are discussed below. Most striking in reference to absorption, distribution, recirculation and excretion is the potential for

TABLE 56

TISSUE DISTRIBUTION OF BROMOBENZENE IN RATS AFTER ORAL ADMINISTRATION OF 750 mg/kg BODY WEIGHT
(Reid et al., 1971b)

Tissue	Bromobenzene concentration 4 hr µg/g ± S.E.	Bromobenzene concentration 24 hr µg/g ± S.E.
Plasma	34 ± 5	2.1 ± 0.4
Liver	282 ± 32	10.7 ± 1.2
Kidney	235 ± 50	18.9 ± 4.6
Brain	206 ± 27	7.0 ± 1.4
Heart	146 ± 21	5.0 ± 1.2
Lung	142 ± 41	6.2 ± 1.0
Stomach	132 ± 37	16.8 ± 6.1
Fat	5,600 ± 900	400 ± 150

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bioaccumulation and cumulative effects if a halogenated compound is not metabolized extensively. Since many of these halogenated benzenes are volatile, they may be continuously lost into the surroundings.

Dibromobenzenes

1,2-Dibromobenzene is absorbed through the gastrointestinal tract. It is also absorbed through intact skin (see reviews in Williams, 1959 and Parke, 1968). As can be seen in Table 58, two major phenolic metabolites have been identified in rabbits, the 3,4- and 2,3-dibromophenols (Ruzo et al., 1976). One other metabolite has not been identified. 1,3-Dibromobenzene is metabolized to four phenolic products: two phenolic isomers were 2,4- and 2,6-dibromophenol (no additional data was given by Ruzo et al. for this isomer).

TABLE 57

BROMOBENZENE METABOLITES IN RAT URINE*
(Zampaglione _et al_., 1973)

Treatment and Dose of Monobromobenzene	Bromophenyl Mercapturic Acid	4-Bromophenol	Bromocatechol	Bromophenyl Dihydrodiol	2-Bromo-phenol
		% of total urinary metabolites			
None					
Nontoxic dose (0.05 mmol/kg)	70 ± 5	18 ± 4	4 ± 2	4 ± 1	3 ± 1
Toxic dose (10 mmol/kg)	48 ± 5	37 ± 4	6 ± 2	4 ± 1	4 ± 1
Phenobarbital					
Nontoxic dose (0.05 mmol/kg)	65 ± 5	21 ± 3	8 ± 2	4 ± 2	1 ± 1
Toxic dose (1.5 mmol/kg)	46 ± 4	36 ± 4	9 ± 2	7 ± 1	1 ± 1
3-Methylcholanthrene					
Nontoxic dose (0.05 mmol/kg)	72 ± 4	14 ± 3	6 ± 2	3 ± 2	4 ± 2
Toxic dose (10 mmol/kg)	31 ± 4	20 ± 3	10 ± 1	17 ± 2	21 ± 2

Nontoxic dose given i.v. as a solution in plasma (0.5 ml).
Toxic dose given i.p. as a solution in sesame oil (1 ml).
Urinary metabolites collected for 48 hours over dry ice.
Values are mean ±SD for eight rats. Recovery of administered monobromobenzenes was >90%.

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1,4-Dibromobenzene is metabolized to a greater extent than 1,2-dibromobenzene. The metabolism of dibromobenzenes is similar to the metabolism of dichlorobenzenes.

TABLE 58

SUMMARY OF RABBIT URINARY METABOLITES OF SOME ISOMERIC BROMINATED BENZENES

Substrate*	Metabolite	% Yield[†]
Bromobenzene	4-Bromophenol	1.2
	3-Bromophenol	1.0
1,2-Dibromobenzene	2,3-Dibromophenol	0.9
	3,4-Dibromophenol	0.9
1,4-Dibromobenzene	2,4-Dibromophenol	1.5
	2,5-Dibromophenol	1.0
1,3,5-Tribromobenzene	2,4,6-Tribromophenol	1.3
	2,3,5-Tribromophenol[‡]	1.1
1,2,4-Tribromobenzene	2,4,5-Tribromophenol	1.0
	2,4,6-Tribromophenol	0.4

* 300 mg was administered to each of two rabbits.

[†] The figure shown is the percent yield of metabolite obtained by extraction and purification of the ether extracts of the hydrolyzed rabbit urine.

[‡] Not conclusively identified due to the unavailability of an authentic standard.

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Higher Brominated Benzenes

1,3,5-Tribromobenzene is metabolized slightly to 2,4,6-tribromophenol and another tribromophenol. Since only one vicinal position is available for direct hydroxylation, the other tribromophenol must be formed via migration of bromine (NIH shift) (Daly et al., 1972). The NIH shift is a molecular rearrangement often accompanied by a 1,2-H or substituents (i.e. Cl, Br, CH_3) shift from site of hydroxylation to the adjacent carbon (Daly et al., 1972). This suggestion is consistent with the concept of an arene oxide intermediate. Similar evidence has been presented for this intermediate in metabolism of dibromobenzene isomers (Ruzo et al., 1976).

1,2,4,5-Tetrabromobenzene yields only trace amounts of a dehalogenated metabolite (Ruzo et al., 1976). These authors also reported that pentabromobenzene yields trace amounts of pentabromophenol and that no data were available for hexabromobenzene.

In summary, lower brominated benzenes are metabolized partially to phenols (see Table 58). Some hydroxylations are accompanied by the migration of bromine, suggesting an arene oxide intermediate. In general, the higher brominated compounds are more resistant to oxidations than the chlorinated compounds, but are metabolically degradable in trace amounts, with products appearing in the urine and feces.

(b) Pharmacology and Metabolism

Background Discussion

Most mammals contain a group of enzymes that specialize in the biotransformation of foreign compounds. These enzymes are located in the endoplasmic reticulum of the liver cells. The metabolic transformation of foreign compounds usually leads to the conversion of lipophilic materials into more polar compounds, which are readily eliminated from the hepatocyte and excreted from the body. Thus, compounds which are of little nutritive value (anutrients or xenobiotics) are prevented from accumulating in cells and tissues. In this way, undesired effects may be avoided (see reviews in Williams, 1959; Parke, 1968).

The endoplasmic reticulum of the cell is the site for the location of many enzymes such as glucose-6-phosphatase, glucuronyl transferase, various steroids, hydroxylases and protein synthetases (Parke, 1972). The enzymes concerned with the metabolism of drugs and other xenobiotics are frequently referred to as mixed function oxidases or monooxygenases. All the monooxygenase drug metabolizing enzymes require reduced nicotinamide adenine dinucleotide phosphate ($NADPH_2$), molecular oxygen and a cytochrome known as P-450. This subcellular structure, endoplasmic reticulum (ER), is not only associated with the oxidation of drugs but also the biosynthesis of cholesterol, the catabolism of bile acids, the oxidation of fatty acids and the oxidation of prostaglandins. In addition to mixed function oxygenase activities, the hepatic endoplasmic reticulum contains a number of reductases, some of which utilize cytochrome P-450 and $NADPH_2$ (Williams, 1959; Parke, 1968).

The biotransformation of drugs and xenobiotics appears to occur in two distinct phases. The first phase includes reactions classified as oxidations, reductions and hydrolyses. In the second phase, the reactions are referred to as syntheses or conjugations. These enzyme reactions, especially oxidations which require cytochrome P-450, have been examined throughout the animal kingdom. Contrary to the suggestion of an evolutionary trend for the appearance of cytochrome P-450 in mammals, this cytochrome is apparently ubiquitous (Ahokas et al., 1976).

However, quantitative differences in metabolism exist for example among livers from various species, among various tissues from a single animal, and between the neonate and adult within a species. It has also been well documented that enzymes of biotransformation may be regulated (stimulated or depressed) by xenobiotics or steroids (Parke, 1972). While there does appear to be a ubiquitous distribution of cytochrome P-450, the concentration in different animal species varies greatly, as can be seen in Table 59. Since these species have differing amounts of cytochrome P-450, they must have different abilities to manufacture toxic intermediates. They also have varying abilities to metabolize benzpyrene and halogenated benzenes.

Species differences in metabolism of monochlorobenzene are shown in Table 60. However, this ability does not appear to be related directly to the concentration of cytochrome P-450 (see Table 59). The postulated rate limiting step in the oxidation of xenobiotic compounds is formation of cytochrome P-450 reductase (Gigon *et al.*, 1968). There is no apparent correlation between this step and the ability to form hydroxy metabolites. Comparing the values for the rabbit in Tables 59 and 60, we observe relatively high levels of cytochrome P-450, low levels of cytochrome P-450 reductase and high ability to form 4-chlorophenol and 4-chlorocatechol. The rat with a high level of cytochrome P-450 reductase has a different pattern of metabolites. Two other factors may determine whether a compound is toxic or not: one is the concentration of enzymes which catalyze conjugation with glutathione and form mercapturic acids, and the other is the concentration of the enzyme epoxide hydrase. The differences above are reflected in the metabolites of chlorobenzene in various species as shown in Table 60.

Pharmacology and Metabolism of Halogenated Benzenes

The lipid soluble halogenated benzenes are distributed throughout mammalian tissues and appear to traverse most tissue barriers including the brain and placenta. As was discussed previously, *o*- and *m*-dihalogenated, 1,2,3- and 1,2,5-trihalogenated and 1,2,3,4-tetrahalogenated benzenes are extensively metabolized.

TABLE 59

SPECIES VARIATION IN THE DISTRIBUTION OF CYT. P-450, P-450 REDUCTASE, NADPH CYT.-C REDUCTASE, AND HYDROXY BENZPYRENE FORMED.

(Kato, 1966; Gigon et al., 1968; Davies et al., 1969; Flynn et al., 1972)

Animal	Sex	Cyt. P-450 nmol/mg	Cyt. P-450 Reductase ‡	NADPH Cyt-c Reductase	Hydroxy benz-pyrene formed
Mouse	M	1.23*	11.2	144	1.82 §
	F	0.86*	12.3	166	-
Rat	M	0.82*	8.4	150	2.92 §
	F	0.67*	7.3	145	-
G. Pig	M	1.10*	3.8	132	2.07 §
	F	1.28*	4.2	145	-
Rabbit	M	1.05*	3.0	130	1.12 §
	F	1.09*	3.4	150	-
Wild Rat	M	0.97†		228	0.14 ¶
	F	0.84†		217	0.04 ¶
Wild R. Monkey	M	1.16†		192	0.11 ¶
	F	1.19†		182	0.10 ¶
Wild S. Monkey	M	0.44†		81	0.15 ¶
	F	0.39†		76	0.19 ¶
Tupaia	M	0.53†		146	0.21 ¶
	F	0.60†		146	0.32 ¶
Pig	M	0.86†		217	0.11 ¶
	F	0.91†		240	0.14 ¶
Man	M	0.28*		70	
	F	0.63*		118	
Trout		0.20		20	

* n mol/mg P

† Δ -A 450-490 per mg P x 10

‡ n mol. product/min/mg P

§ n mol. per mg liver per hr.

¶ n mol. per mg P/min.

TABLE 60

METABOLISM OF ^{14}C-CHLOROBENZENE IN DIFFERENT SPECIES

(Williams et al., 1975)

Species	% of 24 hour excretion of ^{14}C as:		
	4-Chlorophenol	4-Chlorocatechol	4-Chlorophenyl mercapturic acid
Man	33	31	16
Rhesus monkey	19	37	40
Squirrel monkey	14	37	50
Capuchin monkey	19	36	41
Dog	14	45	42
Ferret	33	33	24
Hedgehog	20	12	65
Rabbit	29	38	26
Mouse	20	33	42
Gerbil	13	26	51
Hamster	15	23	43
Guinea pig	27	35	21
Rat	23	22	49

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Some 56% or more of an administered dose of the monohalogenated benzenes are oxidized *in vivo.* As stated in Section (a) above, the oxidized products may be found in the urine as phenols, catechols, sulfates and glucuronides (see Table 51). The main pathway of oxidative metabolism of monohalogenated benzene in the rabbit is an oxidation to phenols and subsequent conjugations. Significant amounts of monofluorobenzene (44%) and monochlorobenzene (27%) are excreted unchanged in the expired air.

There is strong evidence that some of the oxidations proceed through the formation of arene oxides intermediates. Such evidence includes: a correlation of overall toxicity and cellular toxicity with metabolism; a correlation of toxicity with *in vivo* and *in vitro* covalent binding of metabolites with all proteins; and the appearance of increased toxicity associated with a depletion of tissue levels of glutathione (Reid *et al.*, 1973; Reid and Krishna, 1973) (see Table 61).

Monofluorobenzene forms both *o*- and *p*-fluorophenols. In the rabbit the major hydroxy metabolite formed is 4-fluorocatechol (Azouz *et al.*, 1952).

Following a nontoxic dose of monochlorobenzene (0.5g/kg body weight), the urine of rabbits contained dihydrodihydroxybenzene, *p*-chlorophenol and 4-chlorocatechol. The ratio of *p*-chlorophenol to 4-chlorocatechol metabolites was 1:20. Small amounts of *o*- and *p*-chlorophenol were also found. The ratio of glucuronides, ethereal sulfates, mercapturic acids, and unchanged chlorobenzene was approximately 3:3:2:3. The major hydroxy metabolite of chlorobenzene in rabbits was 4-chlorocatechol (Williams, 1959; Parke, 1968). Monobromobenzene has received the greatest attention in metabolic studies. A possible metabolic route for monobromobenzene is shown in Figure 22 (Gillette, 1975a). Following a nontoxic dose of monobromobenzene (210

TABLE 61

EFFECT OF PHENOBARBITAL AND SKF-525A ADMINISTRATION ON COVALENT BINDING OF HALOGENATED BENZENE DERIVATIVES TO RAT LIVER PROTEIN *IN VIVO* 6 HOURS AFTER ADMINISTRATION
(Reid *et al*., 1973.; Reid and Krishna, 1973)

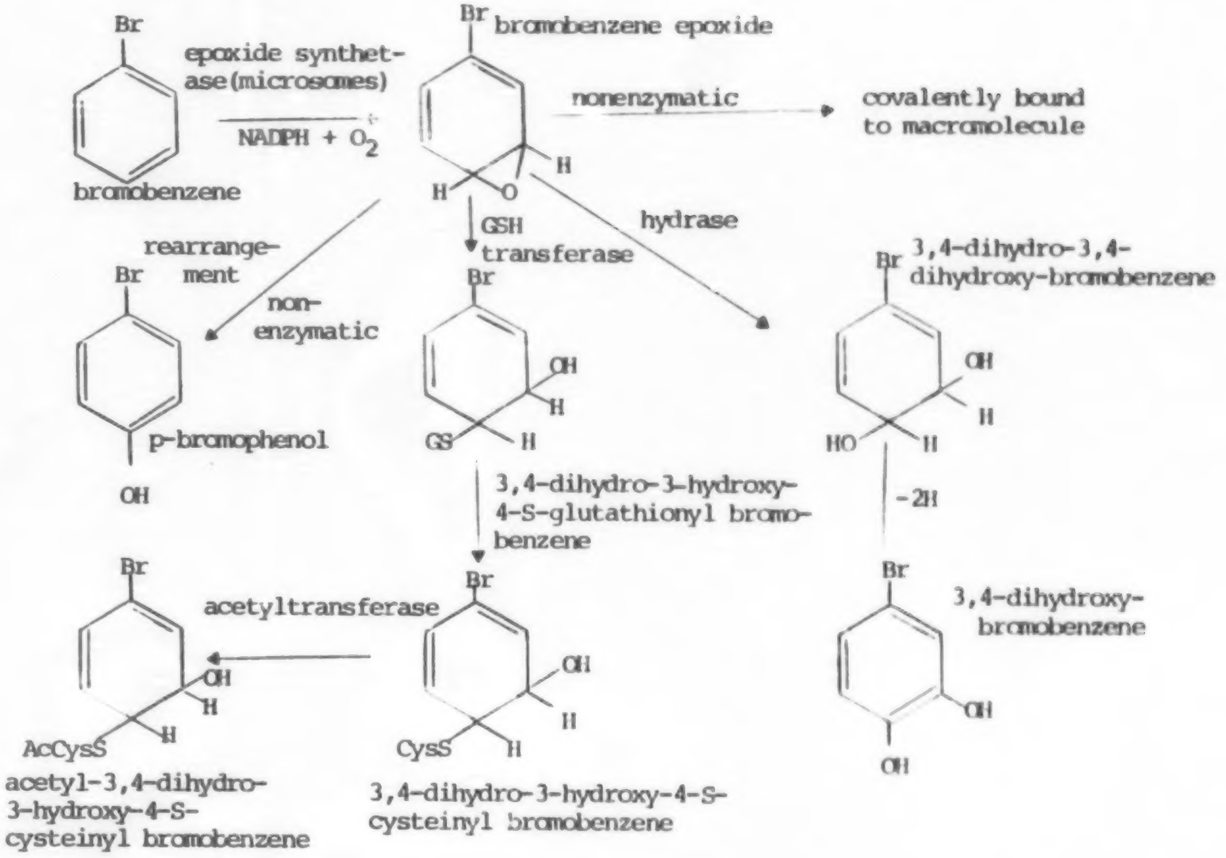
	Control (nM/mg protein ± S.E.)	Phenobarbital (nM/mg protein ± S.E.)	Phenobarbital* SKF-525A (nM/mg protein ± S.E.)
Monobromobenzene-^{14}C (1 mM.kg)	0.267 ± 0.034	0.550 ± 0.031 †	0.036 ± 0.024 ‡
Monochlorobenzene-^{14}C (1 mM/kg)	0.364 ± 0.053	1.268 ± 0.278 †	0.483 ± 0.144 §
Monoiodobenzene-^{14}C (1 mM/kg)	0.090 ± 0.015	0.545 ± 0.129 †	0.666 ± 0.304
Monofluorobenzene-^{14}C (1 mM/kg)	0.085 ± 0.015	0.054 ± 0.008	0.052 ± 0.005
o-Dichlorobenzene-^{14}C (0.5 mM/kg)	0.234 ± 0.015	0.308 ± 0.038	0.186 ± 0.014 §
p-Dichlorobenzene-^{14}C (0.5 mM/kg)	0.021 ± 0.002	0.012 ± 0.001 †	0.006 ± 0.001 ‡

* 2-Diethylaminoethyl-2,2-diphenylvalerate hydrochloride (SKF-525A) (75 mg/kg i.p.) was given 1 hour before the hepatotoxin.

Values are the mean of 6 rats ± S.E.

† $p < 0.01$ compared with controls.
‡ $p < 0.01$ compared with phenobarbital alone.
§ $p < 0.02$ compared with phenobarbital alone.

FIGURE 22 PATHWAYS OF BROMOBENZENE METABOLISM
(Gillette, 1975a)


Br
bromobenzene
epoxide synthetase (microsomes)
NADPH + O2
Br bromobenzene epoxide
H
O
H
nonenzymatic
covalently bound to macromolecule
rearrangement
non-enzymatic
Br
p-bromophenol
OH
GSH transferase
Br
OH
H
GS
H
hydrase
Br 3,4-dihydro-3,4-dihydroxy-bromobenzene
OH
H
HO
H
-2H
3,4-dihydro-3-hydroxy-4-S-glutathionyl bromobenzene
Br
3,4-dihydroxy-bromobenzene
OH
OH
acetyltransferase
Br
OH
H
AcCysS
H
acetyl-3,4-dihydro-3-hydroxy-4-S-cysteinyl bromobenzene
Br
OH
H
CysS
H
3,4-dihydro-3-hydroxy-4-S-cysteinyl bromobenzene

Reprinted with permission, MTP Press, Ltd., St. Leonardgate, England mg/kg body weight) in rabbits, nearly 80% was oxidized to phenols and 20% to p-bromophenylmercapturic acid. The main oxidative product in rabbits was 4-bromocatechol and the minor products were o- and p-bromophenols (see Table 58, Ruzo et al., 1976). The theoretical arguments for the scheme diagrammed in Figure 22 are presented in detail by Gillette (1975a).

For monoiodobenzene, a dose response relationship in rats has been shown for covalent binding, toxicity and extent of metabolism (Azouz et al., 1953). Below 720 mg/kg body weight., there is an increase in mercapturic acid formation with dose. At and above 720 mg/kg body weight, there is a dramatic falloff with a corresponding rise in oxidative metabolites. For the same dose, rabbits form much less mercapturic acid than rats (see Table 60). The major product of oxidative metabolism of monoiodobenzene is 4-iodocatechol. In the rat, p-iodophenol appears to be the major metabolite. Dihydrodihydroxyiodobenzene has also been reported. p-Iodophenol is a minor metabolite in the rabbit (Azouz et al., 1953).

Metabolic products for higher chlorinated benzenes were discussed in the previous section.

(c) Relationship Between Metabolism and Toxicity

Many workers have studied the possibility that occasional cellular damage caused by many drugs is mediated via chemically reactive metabolites. Most of the metabolites formed by the cytochrome P-450 enzymes are chemically inert, but certain of the metabolites such as the arene oxides or epoxides may interact with physiological or biochemical processes, causing either pharmacological or toxicological effects. Investigators are usually able to determine if a response is caused by the parent compound or by one of the metabolites by one of the following procedures (Gillette, 1975a, 1975b):

a) Identify the metabolites and then administer them to the animal.

b) Identify covalent binding of metabolites in tissues.

c) Use inhibitors and inducers of drug metabolism, for either may alter the pattern of effects. Inducers may also increase the metabolism of active metabolites more than they increase the metabolism of the parent compound. This makes it difficult to interpret these studies.

d) Administer drugs chronically to see if the effect on cytochrome P-450 enzymes is biphasic. Almost all of the inducers studied have shown initial inhibition of these enzymes, followed by an increase 12 to 24 hours later. Hence, one substrate seems not only to induce the enzymatic activity for its own metabolism, but also for that of other xenobiotics and steroids.

Inducers of endoplasmic reticulum (ER) drug metabolizing enzymes increased hepatic ER enyzmes when administered to rats for several days. They had little or no effect on other enzymes in the ER (Parke, 1972). On the other hand, hepatotoxic compounds such as halogenated hydrocarbons had an effect on drug metabolizing enzymes, cytochrome P-450 and NADH cytochrome c reductase (Ariyoshi et al., 1975; Carlson and Tardiff, 1976). Glucose 6-phosphatase was shown to undergo a change associated with conformational alteration of ER membranes, which masks an increase in activity of the latent enzyme (Pandhi and Baum, 1970). Induction of hepatic microsomal enzymes by certain carcinogenic hydrocarbons such as 3-methylcholanthrene produces a cytochrome with an absorption maximum at 448 mμ with carbon monoxide as a ligand, whereas the phenobarbital-type is at 450 mμ. The 2- and 4-hydroxylation of biphenyl is stimulated by pretreatment of rats with carcinogenic hydrocarbons, whereas only the 4-hydroxylation is stimulated with phenobarbital-type inducers. Thus, stereospecific hydroxylations and conformational changes in ER membranes may occur following induction (Parke, 1972).

Recent studies of halogenated benzenes, using bromobenzene as a prototype, (Brodie _et_ _al_., 1971; Reid _et_ _al_., 1971b; Mitchell _et_ _al_., 1971) demonstrated that hepatic necrosis produced on exposure to these compounds results from their conversion to reactive toxic intermediates. The stimulation of metabolism of bromobenzene by pretreatment with phenobarbital, potentiates hepatic damage in rats, as can be seen in Table 61. Conversely, blocking metabolism of bromobenzene by SKF-525A (2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride) or piperonyl butoxide (a pesticide synergist) prevents their hepatotoxicity (Reid _et_ _al_., 1973; Reid and Krishna, 1973).

Several studies have shown that bromobenzene induced hepatic necrosis results from the arene oxide reacting with cellular macromolecules. The severity of liver necrosis correlates well with the extent of covalent binding of metabolites _in vitro_ and _in vivo_ after various pretreatments, as can be seen in Table 62. Direct kinetic evidence has shown that the 3,4-bromobenzene arene oxide is the reactive hepatotoxic metabolite. These studies have also demonstrated that the bromobenzene arene oxide formed is preferentially conjugated with glutathione (Reid _et_ _al_., 1973; Reid and Krishna, 1973). The glutathione content in the liver is drastically decreased in the presence of large doses of bromobenzene (see Table 62). Conjugation with glutathione is believed to be an important detoxication mechanism. Liver necrosis occurs when glutathione is depleted. Thus, a threshold dose seems to exist for bromobenzene induced necrosis.

Phenobarbital enhanced both the metabolism and the hepatic necrosis

TABLE 62

COVELENT BINDING, HEPATOTOXICITY, AND MERCAPTURIC ACID EXCRETION OF HALOGENATED BENZENE DERIVATIVES

(Reid *et al.*, 1971b; Reid *et al.*, 1973; Reid and Krishna, 1973)

Compound		Covalent binding (nM/mg protein ± S.E.)	Hepatic necrosis	Mercapturic acid excretion	Glutathione concentration (% of control)*
Monobromobenzene	(1 mM.kg)	0.534 ± 0.050†	Yes	3+	67
Monochlorobenzene	(1 mM/kg)	0.604 ± 0.044†	Yes	3+	Not determined
Monoiodobenzene	(1 mM/kg)	0.323 ± 0.054	Yes	3+	66‡
Monofluorobenzene	(1 mM/kg)	0.060 ± 0.004†	No	+	82
o-Dichlorobenzene	(0.5 mM/kg)	0.234 ± 0.015§	Yes	2+	48‡
p-Dichlorobenzene	(0,5 mM/kg)	0.021 ± 0.002§	No	±	101

Values are the mean of 6 rats.

* Glutathione concentration determined 3 hours after administration of the hydrocarbon.

† Killed at 24 hours.

‡ $p < 0.01$ compared with control.

§ Killed at 6 hours.

caused by monobromobenzene. In contrast, 3-methylcholanthrene did not alter the metabolism of bromobenzene, but reduced hepatic necrosis in vivo. The determination of the urinary metabolites of monobromobenzene showed 3-methylcholanthrene caused an increased excretion of bromophenyldihydrodiols and bromocatechols, whereas phenobarbital did not. Thus 3-methylcholanthrene increased the metabolism of the reactive metabolite greater than it did the parent compound (Reid et al., 1971a).

The finding of increased amounts of dihydrocatechols, catechols and 2-bromophenol after administration of toxic doses of bromobenzene to animals pretreated with 3-methylcholanthrene suggests that this pretreatment induces an alternate pathway of metabolism. Hydrases acting on arene oxides may compete with the arene oxide glutathione route for detoxication (see Figure 22, Gillette, 1975a).

Species differences in bromobenzene's hepatotoxicity and metabolism are summarized in Table 63. As can be seen in this table, intraperitoneal administration of monobromobenzene (1 ml/kg body weight) resulted in extensive centrolobular necrosis in mice and rats, while no specific lesions were detected in neonatal rats, hens, toads and frogs. No definite conclusions regarding the metabolism and toxicity of monobromobenzene in humans can be drawn from these data.

Just as there are species differences in metabolism, there are differences in the metabolism of a halogenated benzene in different organs, i.e., lung may differ from kidney which differs from liver, etc. (see Tables 64 and 65). As can be seen in Table 65, phenobarbital does not increase covalent binding in the lung as shown for the liver (Reid et al., 1973; Reid and Krishna, 1973).

TABLE 63

SPECIES DIFFERENCES IN BROMOBENZENE'S HEPATOTOXICITY AND METABOLISM
(Mitchell et al., 1971)

	Severity of Centrolobular Necrosis	24 hr Bromobenzene Concentration	
		Plasma (ug/ml)	Liver (ug/ml)
Mouse	Extensive	1.0 ± 0.1 (4)	18 ± 4 (4)
Rat	Extensive	2.8 ± 0.3 (7)	26 ± 3 (7)
Rabbit	Minimal to moderate	-	35 ± 12 (3)
Hamster	Minimal to moderate	3.2 ± 0.5 (3)	42 ± 9 (3)
Neonatal rat	No specific lesions	3.8 ± 0.3 (6)	89 ± 24 (6)
Hen	No specific lesions	6.9 ± 1.1 (7)	214 ± 39 (7)
Toad	No specific lesions	-	151 ± 34 (6)
Frog	No specific lesions	-	1701 ± 106 (6)

Animals were given bromobenzene (1 ml/kg, intraperitoneal injection) and killed after 24 hr. Livers were examined histologically and bromobenzene concentrations in plasma and liver were assayed. Values are means ±S.E. with number of experiments in parentheses.

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Phenobarbital or 3-methylcholanthrene enhance the activity of Δ-aminolevulinic acid (Δ-ALA) synthetase, the rate-limiting factor in the enzymatic synthesis of porphyrins. Some porphyrins are intermediates in the synthesis of cytochromes. Porphyria, a disturbance in porphyrin metabolism, is characterized by increased formation and excretion of porphyrin precursors, cutaneous photosensitivity, frequent hemolytic anemia and splenomegaly. Acute abdominal and nervous system manifestations may also occur. In 1959, an outbreak of porphyria in humans was traced to the ingestion of wheat which had been previously treated with hexachlorobenzene. Since that time, hepatic

TABLE 64

DISTRIBUTION OF COVALENTLY BOUND ^{14}C-BROMOBENZENE IN THE MOUSE *
(Reid *et al*., 1973)

Tissue	Covalent binding (nmoles/mg protein)
Liver	1.890
Kidney	1.338
Lung	0.345
Plasma	0.130
Ileum	0.113
Spleen	0.061
Heart	0.049
Stomach	0.049
Brain	0.031
Testis	0.030

* Mice were killed 24 hrs. after administration of a hepatatoxic dose of ^{14}C-bromobenzene (4.8 mmoles/kg).

TABLE 65

BINDING OF AROMATIC HYDROCARBONS IN RAT LUNG: EFFECT OF PHENOBARBITAL*
(Reid *et al*., 1973)

Compound	Time of Killing (hour)	Binding of Hydrocarbon in Lung (mμmole/mg protein)	
		Control	Phenobarbital
Bromobenzene-^{14}C, 1mM/kg	6	141 ± 18	77 ± 7.6 †
	24	117 ± 14	88 ± 7.4
Chlorobenzene-^{14}C, 1mM/kg	6	268 ± 60	172 ± 20
	24	164 ± 26	91 ± 4.0 ‡
o-Dichlorobenzene-^{14}C, 0.5mM/kg	6	27.3 ± 1.4	18.9 ± 2.7 §
	24	20.9 ± 2.4	15.3 ± 2.2
p-Dichlorobenzene-^{14}C, 0.5 mM/kg	6	4.6 ± 0.2	3.4 ± 0.5
	24	3.4 ± 0.4	1.8 ± 0.2

*Values are the means ± SE of 6 animals.

† $p < 0.01$

‡ $p < 0.02$

§ $p < 0.05$

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porphyria has been produced in rats and rabbits by feeding them hexachlorobenzene.

After the addition of 0.25% hexachlorobenzene in the diet of rats, porphyria was produced in 6 to 12 weeks (Lui and Sweeney, 1975). Also occurring were an increase in liver weight, an increase in smooth ER induction of cytochrome P-450 and hepatocellular damage. Evidence was presented that pentachlorophenol is formed during metabolism.

The pentachlorophenol metabolite was found also in the monkey after HCB administration (Yang _et al_., 1975). Rimington and Ziegler (1963) showed that in rats chronic administration of 500 to 800 mg/kg body weight of chlorinated benzenes (except pentachlorobenzene) leads to a hepatic porphyria characterized by elevated levels of precursor porphyrins in liver and feces. The first signs of intoxication were an increase in urinary coproporphyria and porphobilinogen (PBG). Aminolevulinic acid excretion was a late effect. The most active compounds were _p_-dichlorobenzene, 1,2,4-trichlorobenzene and 1,2,3,4-tetrachlorobenzene (see Tables 66 and 67). Histologic examination showed liver necrosis and fatty changes over large areas. Mono-, 1,2-di- and 1,2,4-trichlorobenzene were the most toxic.

After administration of 1,2,4-trichlorobenzene, liver glutathione content was found to have decreased in starved rats. Glutathione given to these highly porphyric rats had a protective effect (Rimington and Ziegler, 1963).

In additional studies, all the chlorinated benzenes were shown to produce distubances in porphyria. If the studies with chlorinated benzenes could serve as a prototype for other halogenated benzenes, it might be said that the severity of this biochemical lesion should vary with both dose and compound. The mechanism for the unique biochemical lesion produced seems similar

TABLE 66

MEAN PEAK VALUES OF URINARY PORPHYRINS AND PORPHYRIN PRECURSORS FOLLOWING TREATMENT OF MALE RATS WITH THE MAXIMUM DOSES TRIED OF EACH CHLORINATED BENZENE; VALUES FOR ALLYLISOPROPYLACETAMIDE AND SEDORMID ARE GIVEN FOR COMPARISON

(Rimington and Ziegler, 1963)

No. of rats	Compound	Sol-vent	Max. dose (mg/kg)	Days on max. dose	Copro-porphyrin (µg/day)	Uropor-phyrin (µg/day)	PBG (µg/day	ALA (µg/day)	ALA PBG
	Controls*	C			4.3-6.8	0.1-0.3	2.5-6.5	38.7-51.6	
3	Monochlorobenzene	P	1140	5	30.50	1.40	26.70	56.40	2.98
3	1,2-Dichlorobenzene	P	455	15	43.10	2.01	26.65	11.32	2.11
3	1,4-Dichlorobenzene	P	770	5	61.80	10.99	1328.10	437.41	0.36
3	1,2,3-Trichlorobenzene	C	785	7	36.59	0.72	57.38	36.26	1.01
3	1,2,4-Trichlorobenzene	C	730	15	58.31	2.73	179.00	145.70	1.06
3	1,2,3,4-Tetrachlorobenzene	P	660	10	28.96	3.80	520.63	315.78	0.61
6	1,2,4,5-Tetrachlorobenzene	C	905	5	4.10	0.22	6.50	18.08	6.69
3	AIA	Pr.g	250	10	17.35	5.00	863.67	571.45	0.71
2	AIA	Pr.g	500	6	43.07	16.61	2539.61	2378.68	0.96
4	Sedormid	Pr.g	250	10	8.32	3.60	851.56	444.99	0.52

P = liquid paraffin; C = 1% cellofas; Pr.g = propylene glycol; AIA = allylisopropylacetamide; PBG = porphobilinogen; ALA = Δ-aminolevulic acid.

* Mean max. and min. of 5 rats during 41 days.

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TABLE 67

PORPHYRINS, PORPHOBILINOGEN AND CATALASE ACTIVITY IN LIVERS OF RATS TREATED WITH CHLORINATED BENZENES, ALLYLISOPROPYLACETAMIDE OR SEDORMID

(Rimington and Ziegler, 1963)

No. of rats	Compound	Max. dose (mg/kg)	Days on max. dose	Copro-porphyrin (µg/100 g)	Protopor-phyrin (µg/100 g)	Uropor-phyrin (µg/100 g uncorrected)	PBG	Catalase (m.eq. mg) wet wt.
	Controls*			4.5	9.7	1.3	—	0.85
2	Monochlorobenzene	1400	5	Trace	13.00	6.35	—	0.502
2	1,2-Dichlorobenzene	450	15	10.05	34.80	14.40	—	0.364
2	1,4-Dichlorobenzene	770	5	5.07	60.50	60.35	—	0.880
2	1,2,3-Trichlorobenzene	780	7	2.65	3.55	20.00	—	0.857
5	1,2,4-Trichlorobenzene	500	10	42.56	55.60	52.70	++	0.747
3	1,2,3,4-Tetrachlorobenzene	660	10	35.04	56.57	41.32	+	0.772
2	1,2,4,5-Tetrachlorobenzene	850	5	6.30	9.90	2.15	—	0.838
3	AIA	250	10	17.35	19.10	13.08	++	0.320
1	AIA	500	6	73.60	114.50	18.49	++	0.140
2	Sedormid	250	10	9.29	12.91	17.07	++	0.220

AIA = allylispropylacetamide; PBG = porphobilinogen.

* Mean of 2 rats.

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to that seen following administration of other inducers of drug metabolism. It is also similar to that seen in man following exposure to ethanol, synthetic estrogens and progesterins (Parke,1972).

Ariyoshi _et al_. (1975) have shown an initial increase in content of cytochrome P-450 and an initial decrease in Δ-ALA synthetase activity following oral administration of chlorinated benzenes. They also reported a dose-response relationship. In the time course after a single oral dose of 250 mg/kg body weight, the activity of Δ-ALA synthetase decreased at six hours, was normal at 12 hours and increased at 24 hours. The opposite changes were noted in the content of cytochrome P-450 (see Table 68). The spectral change in cytochrome P-450 is of the phenobarbital type (Type I).

Carlson and Tardiff (1976) studied the effects of chlorobenzene; 1,4-dichlorobenzene, 1-bromo-4-chlorobenzene, 1,2,4-trichlorobenzene and hexachlorobenzene on adult male rats for 14 days at low doses from 10 to 40 mg/kg body weight.

All halogenated benzenes except monochlorobenzene decreased hexabarbital sleeping time immediately and/or 14 days following treatment. As can be seen in Table 69, cytochrome c reductase, cytochrome P-450 content, _O_-ethyl _O_-_p_-nitrophenyl phenylphosphonothioate (EPN) detoxication, glucuronyl transferase, benzpyrene hydroxylase and azoreductase were increased to varying degrees (Carlson and Tardiff, 1976). Administration of 1,4-di- and 1,2,4-trichlorobenzene for 90 days resulted in an increase in EPN detoxication, benzyprene hydroxylation and azoreductase. The increases were still apparent 30 days later. 1,2,4-Trichlorobenzene was the most potent inducer of cytochrome c reductase and cytochrome P-450. Either no change or a decrease was reported for glucose-6-phosphatase and isocitrate dehydrogenase

TABLE 68

EFFECT OF CHLORINATED BENZENES ON AMINOLEVULINIC ACID SYNTHETASE AND CYTOCHROME P-450 CONTENT OF RAT LIVER *

(Rimington and Ziegler, 1963; Poland *et al*., 1971; Ariyoshi *et al*., 1975; Williams *et al*., 1975)

Chlorinated benzene	Free vicinal positions	Possibility of epoxide formation	Extent of metabolism	P-450 n moles/g	ALA Synthetase n moles/g/hr	Porphyria ‡
Control				0.68	22.6	
Monochlorobenzene	2,3,4,5,6	+	High	0.56	49.2	yes (1140)
1,2-Dichlorobenzene	3,4,5,6	+	High	0.66	36.3†	yes (455)
1,3-Dichlorobenzene	4,5,6	+	High	0.77	29.8†	-
1,4-Dichlorobenzene	2,3,5,6	+	High	0.73	32.3	yes (770)
1,2,3-Trichlorobenzene	4,5,6	+	High	0.84	33.6	yes (785)
1,2,4-Trichlorobenzene	5,6	+	High	1.63	47.5†	yes (730)
1,3,5-Trichlorobenzene	None	-	Low	0.73	34.8	-
1,2,3,4-Tetrachlorobenzene	5,6	+	High	0.97	33.3†	yes (660)
1,2,3,5-Tetrachlorobenzene	None	-	Low	1.14	35.4†	-
1,2,4,5-Tetrachlorobenzene	None	-	Low	0.99	27.5	-
Pentachlorobenzene	None	-	Very low	1.16	98.7†	-
Hexachlorobenzene	None	-	Very low	0.97	51.8	yes (400)

* Rats were pretreated orally with 250 mg/kg body wt. for three days and were sacrificed 24 hours after the last dose.

† Significantly increased over control.

‡ Numbers in parenthesis indicate dose in mg/kg body wt. used to produce porphyria in 5 days. [note: glutathione reduces porphyria produced by halogenated benzenes.]

TABLE 69

EFFECT OF CHLORINATED BENZENES ADMINISTERED po FOR 14 DAYS ON VARIOUS PARAMETERS OF XENOBIOTIC METABOLISM

(Carlson and Tardiff, 1976)

Compound	Dose (mg/kg/day)	Cytochrome c reductase (nmol cytochrome c reduced/min mg protein)*	Cytochrome P-450 (ΔE/mg protein x 10)	Glucuronyl-transferase (nmol/min/mg protein)	EPN † detoxication (μg p-nitrophenol/ 50 mg/30 min)	Benzpyrene hydroxylase (nmol/min/mg protein)	Azoreductase (ng/min/mg protein)
Monochlorobenzene	0	100 ± 25	236 ± 20	5.8± 0.4	6.7± 0.6	1.39± 0.43	
	200	110 ± 8	209 ± 10	9.4± 0.6	7.1± 0.5	0.89± 0.05	
	400	109 ± 9	197 ± 14	12.2± 0.3	8.4± 0.9	0.92± 0.04	
	800	78 ± 5	133 ± 15	13.0± 0.5	7.4± 0.7	0.78± 0.16	
1,4-Dichlorobenzene	0	156 ± 9	178 ± 20	5.9± 0.6	6.7± 0.6	2.36± 0.49	63.9 ± 2.8
	10	151 ± 6	174 ± 15	7.8± 0.6	7.2± 0.6	1.75± 0.13	67.5 ± 2.5
	20	165 ± 8	167 ± 11	11.3± 1.0	9.5± 1.1	3.53± 0.68	71.4 ± 4.3
	40	176 ± 10	193 ± 13	9.6± 0.6	9.0± 0.5	2.15± 0.34	79.2 ± 6.6
1-Bromo-4-chlorobenzene	0	149 ± 22	205 ± 35	5.8± 1.4	9.5± 0.8	1.51± 0.20	59.1 ± 2.5
	10	126 ± 6	180 ± 7	5.6± 0.8	11.4± 0.9	1.37± 0.17	60.9 ± 2.6
	20	123 ± 4	202 ± 7	9.0± 0.7	12.4± 1.1	2.06± 0.26	69.7 ± 4.2
	40	141 ± 5	245 ± 19	9.1± 0.5	14.4± 0.6	2.35± 0.23	79.4 ± 2.7
1,2,4-Trichlorobenzene	0	103 ± 8	72 ± 13	5.0± 0.4	5.8± 0.3	2.82± 0.53	72.4 ±11.1
	10	139 ± 15	99 ± 18	5.1± 0.4	10.3± 0.9	3.82± 0.65	102.0 ± 2.7
	20	192 ± 12	212 ± 45	8.6± 1.6	12.0± 0.8	5.37± 1.01	91.1 ± 4.6
	40	183 ± 9	268 ± 15	8.3± 0.7	15.4± 0.4	5.22± 1.14	130.7 ± 5.3
Hexachlorobenzene	0	85 ± 7	128 ± 18	6.3± 1.0	5.3± 0.9	2.79± 0.54	122.0 ±24.9
	10	106 ± 10	204 ± 18	4.5± 0.5	15.0± 1.1	4.76± 0.58	187.7 ± 7.4
	20	109 ± 7	190 ± 16	6.8± 0.3	18.4± 0.8	4.08± 0.37	210.0 ± 7.4
	40	100 ± 7	150 ± 27	6.6± 0.8	18.9± 0.7	4.24± 0.82	262.7 ±19.1

* Value is mean ± S.E. for group of six rats except for benzpyrene hydroxylase group receiving 40 mg/kg of 1,2,4-trichlorobenzene. In that group, there were five rats.

† EPN - O-ethyl O-p-nitrophenylphenylphosphonothioate

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activities.

These findings demonstrate the ability of halogenated aromatic compounds at low doses to induce enzyme systems associated with the metabolism of foreign compounds. This type of action may influence the metabolism of endogenous steroids, other foreign compounds and drugs. Indirect evidence has been presented which suggests that 1,2,4-trichlorobenzene persists in the animal for some time, continually influencing drug metabolism (Carlson and Tardiff, 1976).

(d) Acute Toxicity

The toxicity of the halogenated benzenes may be influenced by the route of administration whether inhalation, skin absorption, or ingestion. Possibly more important are the solutions or forms in which a halogenated benzene is suspended and/or applied. Most of the halogenated benzenes are less toxic than benzene except possibly monochlorobenzene. All of the halogenated benzenes, like benzene, produce an array of central nervous system effects when administered orally. Among these CNS effects are either stimulation and/or depression.

Most monohalogenated benzenes were shown to produce narcosis. Monofluoro-, monochloro-, monobromo- and monoiodobenzene produced varying degrees of sedation, analgesia and anesthesia after oral or parenteral administration. Relatively large doses of monohalogenated benzenes are necessary to produce acute poisoning as can be seen in Tables 70 and 71. However, chronic effects may occur at relatively low doses. Acute poisoning is characterized by symptoms primarily originating in the nervous system. There may be hyperexcitability, restlessness, muscle spasms or tremors followed by varying degrees of CNS depression. The most frequent cause of death is respiratory failure.

TABLE 70 ACUTE TOXICITY DATA
(U.S. Public Health Service, 1975)

Chemical	Animal	Route	LD50 mg/kg	LC50 mg/kg	LDL$_o$ mg/kg	LCL$_o$ mg/kg
Monochlorobenzene	Rat	Oral	2,910	-	-	-
	Rat	s.c.	4,000	-	-	-
	Rabbit	Oral	2,830	-	-	-
o-Dichlorobenzene	Rat	Inhal.	-	-	-	707 ppm/7H
	Mouse	i.v.	-	-	520	-
	Rabbit	i.v.	-	-	330	-
	Guinea pig	Inhal.	-	-	2,000	-
	Guinea pig	Inhal.	-	-	-	800 ppm/24H
p-Dichlorobenzene	Human	Oral	-	-	TD 300	-
	Rat	Oral	500	-	-	-
	Rat	i.p.	2,500	-	-	-
	Mouse	Oral	2,950	-	-	-
	Guinea pig	Oral	-	-	2,800	-
1,2,4-Trichlorobenzene	Rat	Oral	756	-	-	-
	Mouse	Oral	766	-	-	-
	Mouse	i.p.	-	-	500	-
1,2,4,5-Tetrachlorobenzene	Rat	Oral	1,500	-	-	-
	Mouse	Oral	1,035	-	-	-
Hexachlorobenzene	Rat	Oral	3,500	-	-	-
	Mouse	Oral	4,000	-	-	-
	Cat	Oral	1,700	-	-	-
	Rabbit	Oral	2,600	-	-	-
1,3,5-Trichloro, 2,4,6-trifluorobenzene	Rat	Inhal.	-	- - -	-	380
Monofluorobenzene	Mouse	Inhal.	-	-	45mg/m^3/2H	-
Difluorobenzene	Mouse	Inhal.	-	-	55mg/m^3/2H	-
Hexafluorobenzene	Mouse	Inhal.	-	-	95mg/m^3/2H	-
1-Fluoro-2-bromobenzene	Rat	Oral	1,850	- -	-	-
1-Fluoro-3-bromobenzene	Rat	Oral	670	- -	-	-

LDL$_o$ - Lowest published lethal dose
LCL$_o$ - Lowest published lethal concentration
TD - Toxic Dose

Table 71 ACUTE TOXICITY DATA

Chemical	Animal	Route	LD50 mg/l	LC50 mg/l	Reference
Monochlorobenzene	White mouse	Oral	1,445	-	Varshavskaya, 1967
	White rat	Oral	2,390	-	
	Rabbit	Oral	2,250	-	
	Guinea pig	Oral	5,060	-	
	Mouse	Inhal.	-	20	Rozenbaum *et al.*, 1947
Monochlorobenzene	Guinea pig	Inhal.	-	0.05	Lecca-Radu, 1959
o-Dichlorobenzene	Mouse	Oral	2,000	-	Varshavskaya, 1967
	Rat	Oral	2,138	-	
	Rabbit	Oral	1,875	-	
	Guinea pig	Oral	3,375	-	
p-Dichlorobenzene	Mouse	Oral	3,220	-	Varshavskaya, 1967
	Rat	Oral	2,512	-	
	Rabbit	Oral	2,812	-	
	Guinea pig	Oral	7,593	-	
p-Dichlorobenzene	Mouse	s.c.	5,145	-	Irie *et al.*, 1973
1,2,4-Trichlorobenzene	Rat	Oral	756	-	Brown *et al.*, 1969
	Mouse	Oral	766	-	
	Rat	Percut.	6,139	-	
1,2,4,5-Tetrafluorobenzene	Mouse	Inhal.	-	4.5%	Neal and Robson, 1966
Pentafluorobenzene	Mouse	Oral	710	-	Lapik, 1965
Pentafluorobromobenzene	Mouse	Oral	959	-	Lapik, 1965
Pentafluorochlorobenzene	Mouse	Oral	1,250	-	Lapik, 1965
Monobromobenzene	Rat	Oral	1,600	-	Eastman Kodak, 1976
Monoiodobenzene	Rat	Oral	400-3200	-	
Hexabromobenzene	Mouse	p.o.	14.28 g/kg	-	Kitagawa *et al.*, 1975
Monofluorobenzene	Rat	Oral	4 g/kg	-	Olin Chemicals, 1974
Monofluorobenzene	Mouse	Inhal.	-	45 mg/l*	Olin Chemicals, 1974
Pentafluorobenzene	Mouse	Oral	710	-	Olin Chemicals, 1974
Bromopentafluorobenzene	Mouse	Oral	959	-	Olin Chemicals, 1974
Chloropentafluorobenzene	Mouse	Oral	1,250	-	Olin Chemicals 1974

* Median lethal conc.

Halogenated benzenes like aliphatic halogenated hydrocarbons are thought to sensitize the myocardium to catechol amines, and thus set up conditions favoring ventricular arrhthmyias (Von Oettingen, 1955).

Monochlorobenzene has been studied extensively by most routes of administration and in different species. Monochlorobenzene does not appear to have a high acute toxicity, when administered orally or parenterally. In rats, subcutaneous injection of 4 to 5 g/kg body weight caused no immediate effect, but resulted in death within a few days. On autopsy, the rats were found to have necrosis in liver and kidneys. Larger doses in rats produced CNS depression and acute ataxia. Between 7 to 8 g/kg body weight were fatal in a few hours (Von Oettingen, 1955). In rabbits, monochlorobenzene produced potent CNS depression. The toxic dose of the vapor was 20 mg/l while that for benzene was 30 mg/l. Table 72 presents data from a comparative study of the acute toxicity of benzene and MCB (Rozenbaum _et al_., 1947).

Descriptions of acute pharmacological effects from doses of bromobenzene are scarce in the large volume of literature found on this compound. Bromobenzene may cause depression or "apparent" stimulation of the CNS depending on the dose. Koch-Weser _et al_. (1953) reported acute centrolobular necrosis of liver in rats after intraperitoneal injection of 75 to 450 mg/100 g body weight of monobromobenzene. In rabbits, subcutaneous injection of 2 cc of monobromobenzene resulted in an increase in hemoglobin, erythrocytes and leucocytes and an initial relative lymphocytosis followed by a relative pseudoeosinophilia.

_o_-Dichlorobenzene is toxic in many species of mammal, the extent of toxicity depending on the species and route of administration. Doses of 0.25 to 0.5 cc/kg body weight administered intravenously to rabbits were

TABLE 72 A COMPARATIVE STUDY OF THE TOXICITY OF BENZENE AND MONOCHLOROBENZENE
(Rozenbaum *et al.*, 1947)

Chemical	Animal	Dose	Duration	Route	Weight Loss	CNS	Blood Dyscrasias	Patho-histol.	Deaths	Remarks
Benzene	Rabbits	0.9 mg/kg body wt.	2-20 injections over a 2 week period	s.c.	++ (24-30%)	+d	++	++	4/4	At 2,3,6 & 11 injections, % of hemoglobin & no. of erythrocytes noticeably reduced. Marrow - almost complete aplasia
Benzene	Mice (40)	5-30 mg/l	2 hrs.	Inhal.		+d			42%	Death due to paralysis of respiratory center
									*30 mg/l	Clonic & tonic spasms preceding death.
Monochloro-benzene	Mice (40)	5-30 mg/l	2 hrs.	Inhal.		++d			65%	Narcosis earlier onset & stronger than for benzene
									*20 mg/l	Death due to respiratory failure. Clonic and tonic spasms
Monochloro-benzene	Rabbits	0.9 mg/kg	2-20 inject. over a 2 week period	s.c.	+ (5-16%)	+d	+	+	3/6	1 died after 6 injections; 2 died after 8 injections. Blood - increase in no. of stabnuclear forms and pseudoesinophils, no regular reduction in no. of leucocytes detected. No changes in marrow detected. Kidneys - swelling of epithelium of tubules & glomerules. Liver - swelling, fatty droplets.

* Absolutely lethal concentration
++ Strongly abnormal effect
+ Abnormal effect
d Depression

TABLE 73

THE ACUTE TOXICITY OF FLUORINATED BENZENES -- TEST ANIMAL MICE (250 total)
(Lapik, 1965)

Chemical	Dose	Route	LD_{50}		
			mg/l	mM/l*	
Benzene	10-65 mg/l	Inhal. for 2 hrs.	37	0.47	Tremors of torso, CNS depression, spasms of extremities
Monofluorobenzene	10- 65 mg/l		45	0.46	See benzene above.
o-Difluorobenzene			55	0.48	More severe inhibition of CNS than benzene, monofluorobenzene or the *m*- and *p*- isomers. Breathing deep and slow. Reflexes were weakened.
m-Difluorobenzene			55	0.48	See benzene above
p-Difluorobenzene			55	0.48	See benzene above
Hexafluorobenzene	[10 - 115 mg/l]		95	0.51	
	35 - 40 mg/l				Sedation and sleep
	80 - 90 mg/l				Severe narcosis
	95 - 110 mg/l				Significant inhibition of respiration, heart continued to work for several minutes. Death due to paralysis of repiratory center.

* millimoles/liter

fatal within 24 hours, and doses of 1.00 cc/kg body weight were fatal within 20 seconds (Cameron et al., 1937). Dogs exposed to 2 cc/m^3 (0.04%) showed no adverse effects, whereas 0.08% produced somnolence (Riedel, 1941). Histological studies following administration of acute and 'subacute' doses showed damage to liver and kidneys. Exposing mice to similar concentrations caused CNS stimulation for about twenty minutes followed by CNS depression, muscular twitching, slow and irregular respiration, cyanosis near the end of an hour, and death within 24 hours. Rats and guinea pigs appear more resistant than mice (Riedel, 1941).

p-Dichlorobenzene is much less toxic than o-dichlorobenzene. (LD_{50}'s for both compounds are found in Tables 70 and 71). Rabbits exposed to 4.6 to 4.8 mg/l (770 to 800 ppm) for eight hours per day showed muscular weakness, tremors, nystagmus, edema of cornea and transitory edema of optic nerve. Some died after a few exposures, while a few withstood 62 exposures (Pike, 1944). Rats responded similarly to toxic doses, exhibiting a greater degree of CNS depression and increased irritation of mucosa. Granulocytopenia was also present (Von Oettingen, 1955).

The symptoms of acute toxicity caused by inhalation of several fluorinated benzenes appear in Table 73. The description closely parallels the effects of toxic exposure to chlorinated benzenes. o-Difluorobenzene was shown to be more acutely toxic than benzene, monofluorobenzene or p-difluorobenzene.

Higher fluorinated benzenes have been investigated as potential veterinary anesthetics, and a great deal of data exists evaluating this potential use (Neal and Robson, 1966; Garmer and Leigh, 1967; Hall and Jackson, 1973).

Tetra-, penta- and hexafluorobenzene have received most attention. As can be seen in Table 74, 1,2,3,5-tetrafluorobenzene is the most toxic of the tetrafluorobenzene isomers.

Administration of 0.5% v/v 1,2,3,5-tetrafluorobenzene to mice for 60 minutes did not produce anesthesia, but killed 80% of the mice within 24 to 48 hours. Autopsy showed necrosis of the liver and kidney. 1,2,3,4-Tetrafluorobenzene administered at 0.5% v/v for 50 minutes did produce 12% anesthesia (Neal and Robson, 1966). On autopsy, mice were shown to have centrilobular coagulative necrosis of liver parenchymal cells.

Table 75 summarizes additional testing mainly for hexafluorobenzene. For all animals tested, administration of 4 to 6% v/v hexafluorobenzene resulted in lowered blood pressure. Administration of 4 to 6% v/v hexafluorobenzene resulted in respiratory stimulation in ponies, dogs and sheep and a decrease in respiration in pigs. In cats and dogs, cardiac output decreased (Hall and Jackson, 1973). Garmer and Leigh (1967) and Hall et al. (1975) reported hypotension and bradycardia in cats administered 1.5 to 2.5% v/v hexafluorobenzene. These effects were less marked than after administration of equivalent concentrations of halothane. Recovery from hexafluorobenzene induced anesthesia was similar to recovery from halothane anesthesia for all animals except the cats. The recovery time for cats administered hexafluorobenzene (1.5 to 2.5% v/v) was longer than for halothane anesthesia and was characterized by retching, salivation, ataxia and skin irritation (Garmer and Leigh, 1967; Hall et al., 1975).

(e) Subacute Toxicity

Chronic effects from halogenated benzenes are enlarged livers and cellular degenerations (possible necrosis) in lung, liver and kidney. There may

Table 74 AN EVALUATION OF TETRAFLUOROBENZENES IN ANESTHESIA
(Neal and Robson 1965, 1966)

Chemical	Animal	Premedication	Induction	Dose	Analgesia	Anesthesia	Toxic Effects
1,2,3,4-Tetrafluorobenzene	Mice	None	None	0.5% v/v for 60 min.	+	12%	Centrilobular coagulation necrosis of liver parenchymal cells
1,2,3,5-Tetrafluorobenzene	Mice	None	None	0.5% v/v for 60 min.	+	0%	Most toxic of the three isomers, death of 80% of mice within 24-48 hrs. Necrosis of liver and kidney
1,2,4,5-Tetrafluorobenzene	Mice	None	None	20 minutes at:			
				0.5% v/v	++	-	
				0.25% v/v	+	-	
				2.0% v/v	++	+	
	Dogs	None	Thiopentone (30-50 mg/kg body wt. by i.v.)	4-10% v/v	+	-	
		Morphine (2 mg/kg)	"	8% v/v	+	+	
		Morphine (1.7 mg/kg body wt.) and atropine (0.05 mg/kg body wt.)	"	12% v/v	+	++	Surgical anesthesia for 60 min. (ventricular fibrillation in one dog after only 15 min. inhalation)

++ Highly positive effect
+ Positive effect
+ Weakly positive effect
- No effect

TABLE 75

HEXAFLUOROBENZENE IN ANESTHESIA

Animal	Pre-Medication	Induction	Dose of Hexafluorobenzene	Blood Pressure	Cardiac Effects	Respiration	Recovery	Reference
Ponies (4)	Acepromazine (0.05 mg/kg body wt) and atropine (0.6 mg/kg)	Sodium thiopentone (8-9 mg/kg body wt.)	4% v/v in O_2 (19-45 min) endotracheal intubation	Depression	Initial increase, slow return to normal	Initial stimulation of rate and depth. At high levels, respiratory arrest.	Sweating and salivation, free from excitement	Hall and Jackson, 1973
Dogs (10)	Acepromazine (0.1 mg/kg body wt) and atropine (0.6 mg/kg)	Sodium thiopentone (10 mg/kg body wt.)	5% v/v in 2:1 NO_2/O_2 (endotracheal intubation)	Depression	No cardiac irregularities on electrocardiogram. Slight decrease in rate followed by increase	Increase in rate and depth	Some shivering, 1 excited, generally slow and quiet, no vomiting.2 ate 30 min. after recovery	"
Sheep	none	none	5-6% v/v in NO_2/O_2(by mask, one animal, one by endotracheal intubation	Depression	Increase in heart rate and in cardiac output.	Stimulation	Similar to recovery from halothane	Hall and Jackson, 1973. Hall _et al._, 1975
Pigs (2)	none	Halothane O_2	5% v/v in NO_2/O_2 (endotracheal intubation)	Immediate depression, rapid recovery and then gradual fall	none	Initial stimulation followed by depression, inhalation discontinued after 5 minutes because of depression	More rapidly than halothane	"

TABLE 75 (continued)

Animal	Pre-Medi-cation	Induction	Dose of Hexafluoro-benzene	Blood Pressure	Cardiac Effects	Respiration	Recovery	Reference
Cat (8)	Atropine	4% v/v hexafluorobenzene (by mask)	1.5-2% v/v (by mask)	Depression, less than halothane	None indicated	Depression less than halothane	Longer time than with halothane. 4 cats had conjunctival congestion though faces were not below the mask.	Hall et al., 1975
Cats	———	Thiopentone (20-30 mg/kg)	1.5-2.5% v/v (by mask)	Depression, less than halothane	No spontaneous cardiac arrhythmias	Depression	Long "hang-over" reluctance to move, ataxia, skin irritation. 1 cat - facial edema and conjunctival hyperemia.	Garner and Leigh, 1967

be muscle tremors and hyperirritability. Changes in the metabolism of endogenous steroids may also occur, and if persistent may alter normal levels. The halogenated benzenes are stored in fat; those least metabolized may accumulate or persist in the body. These compounds may alter reactions to stress and bring about cyclic changes (e.g. estrus cycles) or induce changes in gestation and/or reproduction. Halogenated benzenes and endogenous steroids compete for cytochrome P-450 and metabolic degradation. These latter effects have not been studied in detail.

On chronic administration, the halogenated benzenes which induce drug metabolizing enzymes enhance the activity of Δ-aminolevulinic acid synthetase as mentioned previously. This may result in porphyria.

The halogenated benzenes produce blood dyscrasias on chronic administration (see Table 76). Early death, if it occurs, may be due to toxic depression of bone marrow, the pancytopenia leading to hemorrhage and overwhelming infection (Robinson *et al.*, 1975).

Monochlorobenzene

The chronic effects of exposure to monochloro- and monobromobenzene include a decrease in growth rate, and liver, lung and kidney damage (possibly necrosis) and blood dyscrasias. Monochlorobenzene has been shown to interfere with the Schwartzman phenomenon. This is a severe hemorrhagic reaction with necrosis, seen on the abdomen of the rabbit that is first injected with 0.25 cc subcutaneously of typhoid or other culture filtrates, and within 24 hours injected intravenously with 0.01 cc of the same filtrate. The lesion is at the subcutaneous injection site on the abdomen. Whether monochlorobenzene is an immunosuppressant or not needs to be clarified.

While monochlorobenzene reportedly caused leucopenia in rabbits in one study (Cameron et al., 1937), another investigation found an increase in red and white corpuscles after repeated subcutaneous administration of monochlorobenzene (0.9 mg/kg body weight) (Rozenbaum et al., 1947).

Lecca-Radu (1959) showed a change in the regulating influence of the CNS for white rats inhaling 1 mg/m^3 monochlorobenzene for 60 days. Gabor and Raucher (1960) and Tarkhova (1965) also reported abnormalities in alimentary and motor conditioned reflexes in rats after chronic inhalation of MCB (see Table 76).

Dichlorobenzenes

o-Dichlorobenzene was shown to be absorbed and toxic after repeated cutaneous application. The subcutaneous injection of o-dichlorobenzene regularly produced a localized edema and necrosis of adjoining tissue (Riedel, 1941). Repeated subcutaneous administration in rabbits produced blood dyscrasias characterized by agranulocytosis, with little or no effect on red blood cells.

Inhalation of o-dichlorobenzene by rats at 800 ppm for 11 to 50 hours was irritating to eyes and nose, produced slight changes in the tubular epithelium of the kidney, and resulted in confluent massive necrosis of the liver (Cameron et al., 1937). Oral administration to white rats for five months at doses of 0.001 mg/kg to 0.1 mg/kg had a predominant effect on the hematopoietic system and increased prothrombin time (Varshavskaya, 1967). There were also abnormalities in conditioned reflexes.

Rabbits exposed continuously to 100 mg/l of p-dichlorobenzene showed irritation of eyes, nose, muscular twitching, tremors, CNS depression, nystagmus and rapid labored breathing, but recovered within 30 to 120 minutes. Granulocytopenia was present and persisted for three weeks (Zupko and Edwards, 1949). In rats, CNS depression was greater than in rabbits, and irritation of mucous membranes was observed. Of 18 rats administered 100 mg/l for 5 to 9 days, granulocytopenia was confirmed in eight cases, while there was a tendency to granulocytopenia in three additional rats (Zupko and Edwards, 1949). The response of guinea pigs was similar to that of rats and rabbits.

p-Dichlorobenzene reportedly produces histological changes in kidneys, liver, spleen and heart in a number of mammalian species. These changes include cloudy swelling, vacuolization and necrosis (Hollingsworth et al., 1956; Frada and Cali, 1958; Totaro, 1961; Zupko and Edwards, 1949).

Trichlorobenzenes and Tetrachlorobenzenes

Trichlorobenzene (isomer not specified) was fed to rats at a level of 0.01 mg/kg body weight daily for 5 1/2 months. There was an increase in eosinophiles, reticulocytes and leucocytes in the blood, and reduced oxygen consumption (Gurfein and Pavlova, 1962). A dose of 0.003 mg/kg body weight fed daily for 7 to 8 months did not affect conditioned reflexes (Gurfein and Pavlova, 1962).

Tetrachlorobenzene (isomer not specified) was fed to rats at levels of 0.005 and 0.05 mg/kg body weight daily for eight months (Fomenko, 1965). At the lower dosage, there was a change in conditioned reflexes, an increase in the weight coefficient of the liver, and a decrease in -SH groups in blood serum. At the higher level, there was an increase in ascorbic acid content of the organs.

In the same study, 0.05 mg/kg body weight of tetrachlorobenzene was fed daily to rabbits for eight months. There was a tendency toward disorders of glycogen function of the liver, and an initial increase in -SH in blood serum

TABLE 76 CHRONIC TOXICITY DATA

Chemical	Animal	Dose	Duration	Route	CNS	Liver	Blood Dyscrasias	Kidney	Lung	Neoplasia	Remarks	Reference
Monochloro-benzene	White rats	1.0 mg/m3 0.1 mg/m3	24 hrs/day 70-82 days	Inhalation	d d	+ -		+ -	+ -		In kidney caused foci of large cell hyperplasia. Toxic encephalopathy and inflammation of internal organs. Protein dystrophy of liver.	Zhanin, 1969
	Rabbits (6)	0.9 mg/kg body wt.	6-20 shots	Sub-cutaneous	d	+	δ+	+			Weight loss (18-20 shots) 5-16%, 3 deaths after 8 injections. Blood showed increase in number of stab-nuclear forms and pseudoesinophils, no changes in marrow.	Rosenbaum, et al., 1947
	Guinea pigs	0.1 to 1.5 mg/l	Every 2nd day for 3 hrs., 62 wks.	Inhalation			+				Blood-red cells, activity of carbonic anhydrase and indophenol-oxydases lowered at large dose only.	Lecca-Radu, 1959
	White rats (15m)	1 mg/l 0.1 mg/l	60 days 60 days	Inhalation	+ -		+ -				Change in regulating influence of CNS, muscle reflexes abnormal rise in cholinesterase activity. No weight change with either dose.	Lecca-Radu, 1959
Monochloro-benzene	White rats (M)	0.001 mg/kg 0.01 mg/kg 0.1 mg/kg	5 months	Oral	d d d	 +	 +				Change in conditioned reflexes. Predominant effect on hematopoietic system, shift in blood to left, increase in prothrombin time and greater activity of transaminases and alkaline phosphatase.	Varshavskaya, 1967
o-Dichloro-benzene	White rats	0.001 mg/kg 0.01 mg/kg 0.1 mg/kg	5 months	Oral	d	+	+				Predominant effect on hematopoietic system, change in conditioned reflexes. Increase in prothrombin time.	Varshavskaya, 1967
	Rats (10)	800 ppm	11-50 hrs.	Inhalation	d	+		+	-		Confluent massive necrosis of liver. Slight changes in tubular epithelium of kidney. Irritating to eyes and nose.	Cameron et al., 1937
	Rats (10F)	18.8 mg/kg 188 mg/kg 376 mg/kg	5 days/wk. 138 doses in 192 days	Intubation		 δ+ +		 δ+			No adverse effects detected at low dose. Slight increase in average weight of liver and kidney. At high dose, moderate increase in weight of liver, slight decrease in weight of spleen, cloudy swelling of liver.	Hollingsworth et al., 1958

+ = abnormal effect
- = no detected abnormality
δ+ = slight abnormality
d = depressant

TABLE 76 (continued)

Chemical	Animal	Dose	Duration	Route	CNS	Liver	Blood Dyscrasias	Kidney	Lung	Neoplasia	Remarks	Reference
p-Dichlorobenzene	Rats (20M)	341 ppm (2.05 mg/1)	7 hrs/day 5 days/wk., 6 months	Inhalation		δ+	-	δ+	-		Slight increase in average weight of liver and kidney	Hollingsworth et al., 1956
	(5)	173 ppm (1.04 mg/1)	7 hrs/day 5 days/wk., 16 days	Inhalation		δ+	δ+ (F)	δ+	δ+		Slight interstitial edema and congestion of lungs. Slight increase in weight of liver and kidney.	
	(10)	158 ppm (0.95 mg/1)	"	Inhalation		+		+ (m)	-		Cloudy swelling or granular degeneration of liver	
	(10)	96 ppm (0.58 mg/1)	"	Inhalation		-	-	-	-		No abnormalities detected	
	Guinea pigs (3)	125 mg in 50% soln.	10 days	Intramuscular injection			++				Intense steatosis of liver. Weight decrease, lower hepatic glycogen.	Prada and Cali, 1958
	(3)	250 mg	10 days	"			++				Weight decrease, intense steatosis of liver, lower hepatic glycogen	
	Guinea pigs (4)	125 mg/kg 50% w/w olive oil	11 days	"		+	+				Weight loss	
	(4)	125 mg/kg	20 days	"		+	+				Weight loss, increase in level of blood serum transaminase	Totaro, 1961
p-Dichlorobenzene	Mice (10M)	158 ppm (0.95 mg/1)	7 hrs/day 5 days/wk., 157-219 days	Inhalation		-	-	-	-		No abnormalities detected	Hollingsworth et al., 1956
		96 ppm (0.56 ,g/1)	"	Inhalation		-	-	-	-		No abnormalities detected	
	Mice	150 ppm	8 hrs/day 16 days	Inhalation			δ+		δ+		Histology of lungs and liver normal. Shrinkage of nucleus, metachromasia of protoprosm 2 deaths.	Irie et al., 1973
	Rats(2)	10 mg/kg	5 days/wk. for 20 doses	Oral		-	-	-	-			Hollingsworth et al., 1956
	(2)	100 mg/kg				-	-	-	-			
	(4)	500 mg/kg in 10% soln.				-	+	-	-		Marked cloudy swelling and necrosis in central areas of liver lobules	
	Rats (10F)	18.8 mg/kg	5 days/wk., 138 doses in 192 days	Oral			-	-				
		188 mg/kg					δ+	δ+			Increase in weight of liver and kidneys.	
		376 mg/kg					+	+			Increase in weight of liver, kidney, spleen, slight cirrhosis and focal necrosis of liver.	

+ = abnormal effect
- = no detected abnormality
δ+ = slight abnormality
d = depressant

TABLE 76 (continued)

Chemical	Animal	Dose	Duration	Route	CNS	Liver	Blood Dyscrasias	Kidney	Lung	Neoplasia	Remarks	Reference
p-Dichlorobenzene	Guinea pigs (5)	125 g (50%)	20 days	Intramuscular injection	d			+			Weight loss 11.4%. Increase of blood serum transaminases	Totaro and Licari, 1964
	Guinea pigs	125 g (50%)	21 days	"			+				Increase in reaction and clotting formation time	Coppola et al., 1963
	Guinea pigs (8M) (8F)	314 ppm (2.05 mg/1)	7 hrs/day, 5 days/wk., 6 months	Inhalation		+			-		Cloudy swelling, fatty degeneration focal necrosis, slight cirrhosis of liver	Hollingsworth *et al.*, 1956
	(5)	173 ppm (1.04 mg/1)	7 hrs/day, 5 days/wk., 16 days	"		δ+	δ+ (F)	δ+	δ+ (M)		Slight decrease in weight of spleen, slight edema and congestion of lungs	
	White Peking Ducks	0.5% of diet	35 days	Oral							3 deaths after 28 days, no cataracts	
	Rats (19M) (15F)	798 ppm	8 hrs/day, 5 days/wk., doses 1-46 (M) 9-69 (F)	Inhalation	d	+		+ (F)			Tremors, weakness, cloudy swelling of liver. Death: 2M,2F	
	Guinea pigs (16M) (7F)	798 ppm (4.8 mg/1)	8 hrs/day, 5 days/wk., 1-23 (M) 11-20 (F)	"	d	+					Deaths - 2 M	
p-Dichlorobenzene	Rabbits (8M, 8F)	798 ppm (4.8 mg/1)	8 hrs/day 5 days/wk., 1-62 exposures	Inhalation	d	+			+ (2)		Reversible non-specific eye changes	Hollingsworth *et al.*, 1958
	Rabbits (1M, 1F)	173 ppm (1.04 mg/1)	7 hrs/day, 5 days/wk., 16 days	"		-	-	-	δ+		Slight edema and congestion of lungs	
	Rabbits (1M, 1F)	158 ppm (0.95 mg/1)	7 hrs/day, 5 days/wk., 157-219 days	"		-		-	-		No apparent problems detected	
	Rabbits (18M)	100 mg/1 for 30 mins.	5-9 days	Inhalation	d	+	+	+	+		Granulocytopenia 11/18, irritation of mucosa, weight loss 14/18. Tremors, rapid but labored breathing, death 12/18.	Zupko and Edwards, 1949
	Monkey (18)	158 ppm (0.95 mg/1)	7 hrs/day 5 days/wk., 157-219 days	"		-	-	-	-		No apparent adverse effects on organs	Hollingsworth *et al.*, 1956
	Guinea pigs (8)	158 ppm (0.95 mg/1)	"	"		δ+ (F)	-	-	-		Increase in liver weight of female. Decrease in overall wt.	
	(8)	96 ppm (0.58 mg/1)	"	"		-	-	-	-		No adverse reactions detected	
	Guinea pigs (9M)	100 mg/1	5-9 days	"	d	+	+	+	+		Granulocytopenia 5/9, weight loss 6/9, tendency to granulocytopenia 2/9	Zupko and Edwards 1949

+ = abnormal effect
- = no detected abnormality
δ + = slight abnormality
d = depressant

TABLE 76 (continued)

Chemical	Animal	Dose	Duration	Route	CNS	Liver	Blood Dyscrasias	Kidney	Lung	Neoplasia	Remarks	Reference
p-Dichlorobenzene	Wistar rats (9M, 9F)	100 mg/l 20 min.	5-9 days	Inhalation	d	+	+	+	+		Granulocytopenia 8/18, tendency to granulocytopenia, 1/18	Zupko and Edwards, 1949
	Rabbits (5)	1000 mg/kg	92 doses in 219 days	Oral	+	+	+				Loss of weight, tremors, weakness, cloudy swelling and focal necrosis of liver	Hollingsworth *et al*., 1956
	(7)	500 mg/kg	5 days/week for 263 doses	Oral		+	-				Swelling and focal necrosis	"
1,2,4,5-Tetrafluorobenzene	Mice (10)	1%	1/2 hr/day, 5 days	Inhalation		δ+			+		One mouse with bronchitis with severe and extensive acute bronchopneumonia. One mouse - more cytoplasmic vacuolation.	Neal and Robson, 1966
Hexabromobenzene	Mice (M)	0.075 g/kg	Daily, 30 days	Oral		-	-	-	-		No significant pathological changes in heart, lung, kidneys, testis, stomach, small intesting, spleen, lungs, adrenals, thyroid, thymus and cerebrum. Slight lymphocytic infiltration in peripheral area.	Kitagawa *et al*., 1975
		1.75 g/kg				-	-	-	-			
		3.5 g/kg				-	-	-	-			
		7 g/kg				+	-	-	-			
Monoiodobenzene	Rabbits	2 cc	?	s.c.			+				Increase of hemoglobin, red and white blood cells, beginning of relative granulocytosis. Relative pseudo-eosinophilia.	Miyamoto, 1938
Monochlorobenzene	Rats (38)	0.1 mg/l	3 hrs every other day for 37 wks.	Inhalation	+		+				CNS disorders appeared 7th and 14th week; increase in inhibitory process and return to normal state (chronaxy of muscular extensor tibialis), alimentary motor conditioned reflexes abnormal. Blood: abnormal enzymatic activity (peroxidase of leukocytes indophenol-oxidase, carbonic anhydrase).	Gabor and Raucher, 1960

+ = abnormal effect
- = no detected abnormality
δ+ = slight abnormality
d = depressant

TABLE 76 (continued)

Chemical	Animal	Dose	Duration	Route	CNS	Liver	Blood Dyscrasias	Kidney	Lung	Neoplasia	Remarks	Reference
o-Dichlorobenzene	Rats (20)	93 ppm (0.56 mg/l)	7 hrs/day 5 days/wk., 6-7 months	Inhalation		-	-	-	-		No adverse effects judged on gross appearance, organ weights, hematology, urea, and gross and microscopic examination.	Hollingsworth *et al.*, 1958
	(20)	49 ppm	7 hrs/day 5 days/wk., 6 1/2 months	Inhalation		-	-	-	-		"	
	Guinea pigs (8)	93 ppm	7 hrs/day 5 days/wk., 6-7 months	Inhalation		-	-	-	-		Without adverse effects as judged by gross and microscopic examination, hematology and organ weights.	Hollingsworth *et al.*, 1958
	(8)	49 ppm	7 hrs/day 5 days/wk., 6 1/2 months	Inhalation		-	-	-	-		"	
	Rabbits (1M) (18)	93 ppm	7 hrs/day 5 days/wk., 6-7 months	Inhalation		-	-	-	-		"	
	Monkeys (28)	93 ppm	7 hrs/day 5 days/wk., 6-7 months	Inhalation		-	-	-	-		"	
	Mice (108)	49 ppm	7 hrs/day 5 days/wk., 6 1/2 months	Inhalation		-	-	-	-		"	
Monochlorobenzene	Rats (30M)	1 mg/m^3 0.1 mg/m^3	60 days	Inhalation	+		δδ+				Changes in ratio of motor chronaxia of flexor and extensor muscles - reverse ratio due to CNS imbalance. Rise in cholinesterase activity at 1 mg/m^3 only. Total amount of blood serum proteins did not change, no changes in leucocytes. At 1 mg/m^3, lowering of alpha and increase in beta globulins.	Tarkhova, 1965

+ = abnormal effect
- = no detected abnormality
δ+ = slight abnormality
d = depressant

followed by a decrease. There was also an increase in hemoglobin content of blood and in content of reticulocytes in the peripheral blood (Fomenko, 1965).

Hexahalogenated Benzenes

Chronic studies in rats have shown that hexachlorobenzene at a 0.25% level in the diet produced porphyria in 6 to 12 weeks. Other changes were a weight gain, an increase in smooth endoplasmic reticulum, and a reduction of cytochrome P-450 content. Histological changes showed evidence of centrilobular necrosis in liver. This relatively recent report suggests hexachlorobenzene may not be as inert as once thought (Lui and Sweeney, 1975).

Hexabromo- and hexafluorobenzene appear to be less toxic than hexachlorobenzene (Gage, 1970; Hall and Jackson, 1973; Hall *et al*., 1975; Kitagawa *et al*., 1975). In mice fed hexabromobenzene at levels from 0.875 to 7 g/kg body weight daily for 30 days, there was no evidence of necrosis or porphyria even at the highest dosage (Kitagawa *et al*., 1975). Gage (1970) detected no abnormalities in rats exposed to 500 ppm of hexafluorobenzene for 15 six hour exposures. At 1000 ppm for the same period of time he detected reactive hyperplasia in the spleen of rats. Inhalation of mixed hexahalogenated benzenes resulted in narcosis, eye irritations, porphyria in some cases, and nose irritations. Gage (1970) showed a definite increase in subacute inhalation toxicity as successive fluorine atoms in hexafluorobenzene are replaced by chlorine (see Table 77).

(f) Effects on the Eye

As mentioned previously, halogenated benzenes are irritating to eyes and mucosa in varying degrees depending on the compound and extent of exposure. In 1939, there was a report of cataract formation in two women allegedly

TABLE 77 A COMPARISON OF THE SUBACUTE INHALATION TOXICITY OF HEXASUBSTITUTED BENZENE FOR RATS
(Gage, 1970)

Dose (ppm)	No. of Rats	Exposure	Hexafluorobenzene	Chloropentafluorobenzene	1,3-Dichlorotetrafluorobenzene (5% 1,2)	1,3,5-Trichlorotrifluorobenzene	1,2,4-Trichlorobenzene
3000	2M	1 x 30 min	—	—	Eye irritation, nasal discharge, respiratory difficulty, light narcosis	—	—
1000	4M 4F	6 x 6 hr. 4 x 6 hr. 4 x 6 hr.	No wt. gain (F) autopsy (histol.) lungs- macrophages, spleen-reactive hyperplasia	Lethargy. incoordination, no porphyrinuria, autopsy- organs normal	Light narcosis, recovery overnight, increased urinary coproporphyrin (M), porphobilinogen (M&F) histology- damage to kidney tubules	—	—
500	4M 4F	15 x 6 hr	No porphyrinuria blood and urine normal, autopsy- organs normal	Unresponsive, no porphyrinuria, autopsy- organs normal	Light narcosis recovered overnight, retarded wt. gain, blood and urine normal (histology), slight kidney tubular lesions	—	—
380	2M 2F	2 x 6 hr	—	—	—	Nose irritation respiratory difficulty, narcosis, males died. Increase in urinary protein and porphobilinogen, high blood urea. Liver-focal necrosis, centrilobular vacuolation with fatty changes in kidney, tubular necrosis.	—
250	4M 4F	15 x 6 hr	No toxic signs, autopsy - organs normal	—	—	—	—
200	2M 2F	15 x 6 hr	—	—	—	—	Lethargy, retarded wt. gain, autopsy - organs normal
100	4M 4F	15 x 6 hr	—	—	No toxic signs, autopsy - organs normal	—	—
83	4M 4F	15 x 6 hr	—	—	—	No toxic signs blood and urine normal, livers enlarged	—
70	2M 2F	15 x 6 hr	—	—	—	—	Initial lachrymations, lethargy, retarded wt. gain, autopsy - organs normal
50	4M 4F	15 x 6 hr	—	No toxic signs, autopsy - organs normal	—	—	—
20	4M 4F	20 x 6 hr	—	—	—	—	No toxic signs, autopsy - organs normal

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exposed to mothballs containing p-dichlorobenzene (Berliner, 1939). While it was neither confirmed that the cataracts were due to p-dichlorobenzene, nor clear the extent of exposure, several animal studies have concentrated on documenting the effects of chlorinated benzenes on the eye.

Berliner found that no opacity of the lens (of rabbits) was produced on inhalation of p-dichlorobenzene (5 g every two days) daily for 5 to 47 days. After feeding rabbits 5 g daily for three weeks, Berliner found slight to moderate opacity of the lens. Impurities in the chemical (perhaps naphthalene?) might explain this reaction. Other studies seem to indicate that eye changes due to excessive exposure to p-dichlorobenzene (or other chlorinated benzenes) are reversible in nature (see Table 78).

(g) Dermatological Pathology

Available studies are summarized in Table 79. Effects seen on topical administration of 1,2,4-trichlorobenzene to rabbits and guinea pigs included spongiosis, acanthosis, parakeratosis (Brown et al., 1969). No signs of skin sensitization were noted for either species.

(h) Teratogenicity

There were very few studies on the effects of halogenated benzenes in the pregnant mammal. Those found are summarized in Table 80. No teratogenicity studies were found for the chlorinated benzenes in greatest commercial use. Khera and Villeneuve (1975) reported both maternal and fetal accumulation of pentachlorobenzene fed to pregnant rats at doses of 50 to 200 mg/kg body weight/day for the 6th to 15th days of gestation. There was a decrease in fetal weight, significant incidence of extra rib formation, and retarded sternal development at the highest dose.

Courtney et al. (1976) showed a minimal incidence of teratogenic effects

TABLE 78 EFFECTS OF HALOGENATED BENZENES ON THE EYE

Chemical	Animal	Exposure	Effects	Reference
p-Dichlorobenzene	Rabbits	4.6 to 4.8 mg/l (770-800 ppm) for 8 hours, inhalation	Lateral nystagmias, transitory edema of cornea. - edema of optic nerve. Eye changes reversible (17 days). No lens changes or deposits in the vitreous.	Pike, 1944
p-Dichlorobenzene*	2 Women	To moth ball fumes?	(1) both eyes - cataracts, (2) left eye - anterior cortical changes, esp. periphery of lens. Separation of lamellae and severe large water slits.	Berliner, 1939
p-Dichlorobenzene	Rabbits	Inhalation. 5 gm vaporized/2 days 5-47 days	No opacity of the lens (liver necrosis & death)	Berliner, 1939
p-Dichlorobenzene†	Rabbits	Oral, 5 gms PDB daily for 3 weeks	Opacity of lens slight and mod.	Berliner, 1939
o-Dichlorobenzene	Rabbits	2 drops in each eye	Pain slight. Conjunctival irrit. cleared 7 days	Hollingsworth, et al., 1958
1,2,3-Trichlorobenzene	Rabbits	Drops?	Severe pain, conjunctivitis, chemosis & discharge without corneal involvement, lids v. swollen. Conjunctivae inflamed at least 48 hrs. Wash water helped relieve pain.	Brown et al., 1969

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* Purity not established, identity of PDCB not proven.
† Purity not established.

TABLE 79 TOPICAL APPLICATION/DERMATOLOGICAL

Chemical	Animal	Dose	Exposure	Remarks	Reference
o-Dichlorobenzene	Man	—	Topical applic. to skin	After 15 minutes - burning sensation, turned red, more marked after 24 hrs., blisters, brown pigmentation lasting over 3 months	Riedel, 1941
1,2,4-Trichlorobenzene	Man	—	Window sashes treated with ODCB	Watery blisters on face, hands, arms. Disappeared and reappeared w/application. Patch test showed sensitivity to ODCB	Downing, 1939
1,2,4-Trichlorobenzene	Rabbits (4M, 4F)	1 ml, 6 hr/day for 3 days	Covered skin test	Spongiosis, acanthosis, parakeratosis	Brown et al., 1969
	Rabbits (1M, 1F)	1 ml/day (5 days/wk) 3 weeks	Uncovered skin test	Spongiosis, acanthosis, parakeratosis plus some superficial dermis	
1,2,4-Trichlorobenzene	Guinea pig (5M, 5F)	0.5 ml/day for 5 days/wk, 3 wks.	Uncovered skin	Spongiosis, acanthosis, parakeratosis. "Some" deaths. - necrotic foci in liver - no zonal pattern of necrosis	Brown et al., 1969
	Guinea pig	0.1% w/v 3 days/wk for 3 wks. No treatment for 10 days. 11th day challenge	Intradermal or topical	No signs of skin sensitization	Brown et al., 1969

in rats fed hexachlorobenzene (100 mg/kg body weight orally). There was maternal and fetal accumulation of hexachlorobenzene, especially in fatty tissue. Abnormalities detected were an increased incidence of 14th rib formation and sternal defects. It is obvious that more information is needed concerning the effects of hexachlorobenzene on fetal development in mammals.

Khera and Villaneuve (1975) also examined the effects of hexabromobenzene on fetal development in the rat. There was some maternal and fetal tissue accumulation at 200 mg/kg body weight, indicating that hexabromobenzene did pass the placental barrier. No statistically significant evidence of teratogenicity was found.

(i) Mutagenicity/Carcinogenicity

There has been at least one in vitro study of the inhibitory effect of dichlorobenzene (isomer not specified) on the number of mitoses in rat lung cell cultures (Guerin et al., 1971). The dose of 5 µg did not produce any significantly different number of mitoses than the control, i.e. in this test system, dichlorobenzene gave a negative result, it did not exert any inhibitory action on the cultures. No additional mutagenic data were found for mammals, though several chlorinated benzenes are known mutagens for plants and microorganisms (q.v.).

In an earlier study, Guerin and Cuzin (1961) found that dichlorobenzene (isomer not specified) gave a slight response for carcinogenic activity in mice, as measured by the sebaceous gland and the hyperplasia tests. In both cases, dichlorobenzene (1 g/100cc solution in acetone) was applied to the skin of Swiss mice three times (0.1 cc solution). The sebaceous gland test was based on the disappearance of the glands after application of the test compound. The hyperplasia test examined the thickening of the skin epithel-

TABLE 80 THE EFFECTS OF HALOGENATED BENZENES ON THE COURSE OF GESTATION IN MICE AND RATS

Chemical	Animal	Dose mg/kg/day	Maternal Body Wt.	Maternal Body Accum.	Fetal Accumul.	Terato-genic	Description	Reference
Pentachloro-benzene	Rat	200 (6-15 day of gestation)	-	++	++	++	Decrease in fetal wt., extra rib, retarded sternal development	Khera and Villanueve, 1975
		100	-	+	+	+	Extra rib	Villaneuve and Khera, 1975
		50	-	+	+	+	Extra rib	
Pentachloro-benzene	Mouse	*	*	δδ+	None detected	*		Courtney et al., 1976
Hexabromo-benzene	Rat	200 100 50	-	δ+	δ+	Not statist. sig.		Khera and Villaneuve, 1975

++ stronger positive effect
+ positive
δ+ mildly positive
- negative effect

* Please note, this study was to determine the teratogenic effects of pentachloronitrobenzene (PCNB) and hexachlorobenzene (HCB). Pentachlorobenzene (QCB) is a contaminant of both chemicals. Administration of a single oral dose of PCNB (50 mg/kg body wt.) with < 0.1% QCB or HCB (50 mg/kg/day, 7 to 11 days of gestation) with impurity 9.6% QCB in maternal fatty tissue. QCB did not appear in fetal tissue in either test.

ium after application. On an arbitrary scale of 0 to 4 (negative to strongly positive), dichlorobenzene scored 0.9 on the former test, and 0.7 on the latter.

Carcinogenesis has mainly been studied for the lower halogenated benzenes in what appars to be subacute or chronic type studies (Hollingsworth et al., 1956, 1958). These studies were negative. The formation of an arene oxide intermediate has been associated with mutagenesis and carcinogenesis. Since halogenated benzenes form these reactive intermediates, one would have to conclude that these tests are inadequate by today's standards for carcinogenic as well as mutagenic testing. It appears that no carcinogenic tests have been conducted lasting over a year in duration, a short time period according to today's standards.

Murphy and Sturm (1943) studied the effects of p-dichlorobenzene on induced resistance to a transplanted leukemia in the rat. Forty rats were immunized by intraperitoneal injection of either defibrinated rat blood, or chopped 15 day old rat embryo. They were exposed to saturated p-dichlorobenzene vapors for two to three hours daily for 14 days, and then injected with 0.2 cc of leukemia cells.

There were 67.5% animals with tumors in the immunized group exposed to p-dichlorobenzene. An immunized group not exposed recorded 20.5% tumors while the control (no immunization) was 84.2% positive. It would appear that p-dichlorobenzene modified the induced resistance of the rats to the leukemia However, there is not sufficient evidence to state that there are possible immunosuppressant effects resulting from exposure to p-dichlorobenzene.

(j) Behavioral Effects

Gabor and Raucher (1960) and Tarkhova (1965) reported abnormalities in

TABLE 81

CARCINOGENIC AND RELATED STUDIES

Chemical	Test System	Exposure	Result	Remarks	Reference
Pentachlorobenzene	Mice Rats Dog	- - -	Tumors None None	- -	Preussman, 1975
Bromobenzene	Rat Liver	2.5 mg/kg body weight	Neg.	Unlike CCl_4, bromobenzene did not alter polysomal pattern	Sanna *et al.*, 1974
p-Dichlorobenzene	Leukemia in rats	Fumes	-	Modified induced resistance to transplanted leukemia cells. Suggest immunosuppression	Murphy and Sturm, 1943
p-Dichlorobenzene	Irradiated mice	0.2% i.p. in sesame oil with silica	Ascites, sarcoma-like growth	One animal tumor when grafted gave 100% takes	Parsons, 1942
↓	Irradiated mouse	0.2% s.c. with silica	-	-	↓
↓	Control mice	0.2% s.c. in sesame oil with silica	Sarcoma	1 animal	↓

TABLE 82

SUMMARIES OF CARCINOGENIC TESTING OF ORTHODICHLOROBENZENE
(Hollingsworth et al., 1956)

Animal	No.	Strain or Type	Sex	Preparation and Dose	Site or Route	Tumors	Survival	Duration
Rats	17	—	F	93 ppm (0.56 mg/l) of vapor 7 hrs/d., 5 d./wk.; 131 exposures	Inhalation	0	—	190 days
Rats	18	—	M	93 ppm (0.56 mg/l) of vapor 7 hrs/d., 5 d./wk.; 125 exposures		0	—	182 days
Rats	40	—	10ea	49 ppm (0.29 mg/l) of vapor 7 hrs/d., 5 d./wk.		0	—	6 1/2 months
Guinea pig	8	—	M	93 ppm (0.56 mg/l) of vapor 7 hrs/day, 5 d./wk.		0	—	197 days
Guinea pigs	7	—	F	93 ppm (0.56 mg/l) of vapor 7 hrs/day, 5 d./wk.		0	—	199 days
Guinea pigs	16	—	8ea	49 ppm (0.29 mg/l) of vapor 7 hrs/day, 5 d./wk.		0	—	6 1/2 months
Mice	10	—	F	49 ppm (0.29 mg/l) of vapor 7 hrs/day, 5 d./wk.		0	—	6 1/2 months
Rats	10	White	F	376 mg/kg in olive oil, 5 d./wk., 138 doses	p.o. stomach tube	0	9 at 192 days	192 days
Rats	10	White	F	188 mg/kg in olive oil, 5 d./wk. 138 doses	p.o.	0	5 at 192 days	192 days
Rats	10	White	F	18.8 mg/kg in olive oil, 138 doses	p.o.	0	7 at 192 days	192 days

TABLE 83

SUMMARIES OF CARCINOGENIC TESTING OF PARA-DICHLOROBENZENE
(Hollingsworth et al., 1956)

Animal*	No.	Strain or Type	Sex	Preparation and Dose †	Site or Route	Tumors	Survival	Duration
Rats	15	—	F	798 ppm of vapors 8 hrs/d., 5 d/wk., total of 9-69 exposures	Inhalation	0	—	7 months
Rats	20	—	M	341 ppm of vapor 7 hrs/d., 5 d./wk. for 6 months		0	—	6 months
Rats	10	—	—	158 ppm of vapor 7 hrs/d. 5 d./wk. for 157-219 days		0	—	219 days
Rats	10	—	—	96 ppm of vapor 7 hrs/d., 5 d./wk for 6-7 months		0	—	7 months
Rabbits	16	—	M,F	798 ppm of vapor 8 hrs/d., 5 d./wk total of 1-62 exposures		0	4 died	14 weeks
Rabbits	2	—	M,F	158 ppm of vapor 7 hrs/d., 5 d./wk.		0	—	219 days
Rabbits	2	—	M,F	96 ppm of vapor 7 hrs/d., 5 d./wk.		0	—	7 months
Guinea pig	16	—	M	798 ppm of vapor 7 hrs/d., 5 d./wk.		0	2 died	4 1/2 weeks
Guinea pig	8	—	M	341 ppm of vapors 7 hrs/d. 5 d./wk.		0	—	6 months
Guinea pig	8	—	F	341 ppm of vapors 7 hrs/d. 5 d./wk.		0	—	6 months

TABLE 83 (continued)

Animal *	No.	Strain or Type	Sex	Preparation and Dose†	Site or Route	Tumors	Survival	Duration
Guinea pigs	8	—	—	150 ppm of vapor 7 hrs/d., 5 d./wk.	Inhalation	0‡	100%	219 days
Monkey	1	—	F	150 ppm of vapor 7 hrs/d., 5 d./wk.	↓	0‡	—	219 days
Monkey	1	—	F	96 ppm of vapor 7 hrs/d. 5 d./wk.	↓	0	—	7 months
Mice	10	—	M	150 ppm of vapor 7 hrs/d. 5 dd./wk.	↓	0‡	—	219 days
Mice	10	—	F	96 ppm of vapor 7 hrs/d., 5 d./wk.	↓	0‡	—	7 months
Rats	10	White	F	376 mg/kg in olive oil, 5 d./wk for 138 doses	p.o. stomach tube	0§	—	219 days
Rats	10	White	F	188 mg/kg in olive oil, 5 d./wk for 138 doses	↓	0	—	192 days
Rats	10	White	F	18.8 mg/kg in olive oil, 5 d./wk. for 138 doses	↓	0	—	192 days
Rabbits	5	White - colored	M,F	1000 mg/kg in olive oil for 92 doses	↓	0	some deaths	219 days
Rabbits	7	—	—	500 mg/kg fed 5 d./wk. for 263 doses	↓	0	—	219 days
Ducks	10	White-Peking	—	0.5% in diet for 35 days	↓	0	3 died after 28 d.	35 days
Mice	6	Stock	—	0.4 mg in sesame oil	s.c.	0	3 died in 10 days	10 days
Mouse	1	Stock	—	0.4 mg in sesame oil	i.p.	1	3 died in 10 days	10 days
Mice	10	Stock	—	0.4 mg in sesame oil, 9 times	s.c.	1	4 died in 30 days	77 days

* young adult
† min purity, 99%
‡ histopathology negative
§ cirrhosis and hepatic necrosis

conditioned reflexes in rats after chronic inhalation of o-dichlorobenzene. Fomenko (1965) reported a change in conditioned reflexes of rats fed 0.005 mg/kg body weight of tetrachlorobenzene (isomer not specified) for eight months. A similar study with trichlorobenzene did not find any evidence of alteration in conditioned reflexes (Gurfein and Pavlova, 1962).

No other studies on behavioral effects were found. It is reasonable to expect that because of the action of halogenated benzenes on the CNS, that there may be additional behavioral effects not yet described.

(k) Possible Synergisms

The halogenated benzenes as a group appear to interact with cytochrome P-450 in those animal species investigated. In mammals in particular, they seem to stimulate and inhibit drug metabolism, and alter the levels of cytochromes in the cell. Since many compounds, whether they are agricultural and industrial chemicals or drugs, are similarly handled by the cytochrome P-450 system, there would appear to be many possibilities for synergistic as well as antagonistic actions.

Experiments to determine this should be carefully designed. For example, in man phenobarbital has been shown to stimulate the drug metabolism at three to four days. If therapy continues, it appears that the marked stimulation is lost. This has not been taken into consideration in many animal studies, i.e., only the three to four day effect has been studied.

From recent studies in man using identical or fraternal twins, the role of the environment as an explanation for differences in metabolism is being deemphasized in favor of genetic differences. If this is the case, people who have genetic susceptibility to inducible drug-metabolizing enzymes may be more prone to adverse effects, if there is a toxic intermediate or product formed in vivo (Goujon et al., 1972; Vesell et al., 1976). Goujon et al. (1972) found that hexachlorobenzene differentially inhibits aryl hydrocarbon hydroxylase in genetically responsive and non-responsive mice. Similarly, Vesell et al. (1976) showed that the toxicity of chloroform to the kidney is different in genetically susceptible and non-susceptible mice.

It should be emphasized that toxicity is not determined by a single locus gene but may involve multiple loci. For example, epoxide hydrase or glutathione conjugase may also be important in determining toxicity.

Goujon et al. (1972) and Vessell et al. (1976) demonstrated genetically controlled variations in the susceptibility of mice to hexachlorobenzene and chloroform. Hence, exposure to a wide range of environmental contaminants including the halogenated benzenes could affect the ability of these animals to detoxify xenobiotic substances. Synergistic effects of the halogenated benzenes in combination or with other environmental contaminants could be especially damaging for the genetically susceptible individual.

There was one example of synergistic effects of halogenated benzenes on a target organism found in the literature (Hinze et al., 1970). The antifungal activity of halogenated benzenes was synergistic with organo-tin compounds. The mechanism of the toxicity was not discussed. There were no studies found on synergistic effects in mammals or other nonmammalian species.

3. Effects on Other Vertebrates

(a) Fish

(i) Metabolism and Toxicity

Trout have the necessary hepatic enzymes to metabolize halogenated benzenes (see Table 84). The lower homologues can be biotransformed to a greater extent than the polyhalogenated compounds. The concentration of

TABLE 84

HEPATIC LEVELS OF CYTOCHROME P-450 AND NADPH-CYTOCHROME C REDUCTASE ACTIVITY, IN TROUT COMPARED WITH VALUES FOR MAN AND RAT
(Pelkonen _et al._, 1973; Ahokas _et al._, 1976)

	Trout	Man	Rat
Cytochrome P-450 in 12,000 x g supernatant (nmol/g liver)	7	13.6*	31*
NADPH-cyt. c reductase in homogenate (nmol cyt. c reduced/g liver/min.)	2000	3008	3508
In the microsomal fraction:			
Cytochrome P-450 (nmol/mg microsomal protein)	0.2 † 0.17±0.03 §	0.53	0.72
NADPH - cytochrome c reductase (nmol cyt. c reduced/mg microsomal protein/min.)	20† ‡14 ± 3 §	78	96

* Determined from the homogenate.
† Livers pooled from 10 fish.
‡ Individual livers of 8 fish.
§ Mean ± S.D.
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cytochrome P-450 in the trout is lower than in mammalian species. It would appear that the content of the trout microsomal enzyme fraction is lower than in man and rats (see Table 84). As mentioned earlier both the tissue level of epoxide hydrase and glutathionase are important in determining toxicity. Hence, the cytochrome P-450 content alone does not give the information needed for evaluating the toxic potential in fish.

No studies on behavioral effects in fish were found. Here again there is a need for information, especially documenting the effects of long-term, low level doses of specific chlorinated benzenes on the migratory and reproductive behavior of fish.

Leach (1977) is currently investigating the persistence and metabolism of chlorinated benzenes in fish tissue. Rainbow trout are exposed to di-, tri-, tetra- and pentachlorobenzenes. After three weeks, the fish are transferred to fresh water, and monitored to determine how long it takes the fish to excrete the chemicals. A metabolic study is being conducted parallel to the persistence evaluation, and a chronic toxicity evaluation will be undertaken some time in the future. A report is expected from the group by late Spring 1977.

Webber (1977) and his group at Oregon State have just started a structure activity relationship study of the hepatotoxicity of chlorinated benzenes. They will also examine several of the chlorinated nitrobenzenes and selected brominated benzenes. They are using hundreds of inbred guppies for this study. A second study of the impact of hexachlorobenzene on liver function will be conducted with rainbow trout.

Peterson (1977) indicated that his group is interested in a future study of the mechanism of elimination of chlorinated benzenes after administration to fish. He is currently studying the effects of chlorinated benzenes on the liver and the pancreas of rats. An abstract of his work will be available some time this year. Monochlorobenzene, o-dichlorobenzene, the three trichlorobenzene isomers and monobromobenzene altered the excretory functions of both liver and pancreas. p-Dichlorobenzene did not have this effect. Both 3-methylcholanthrene and cystine protected the rats from the toxicity of monobromobenzene.

(b) Amphibians - the Frog

Safe *et al*. (1976) investigated the metabolism of chlorinated benzenes and other chlorinated aromatic compounds in the frog (*Rana pipiens*). A solution of each of the chlorinated benzenes tested (80 mg in 4 to 5 ml of vegetable oil) was administered in four equal aliquots by intraperitoneal injection to each of four frogs. The frogs were provided with water (250 ml) but no food. After four days, the water was changed, and after eight days both samples of water were analyzed. Metabolites were extracted with chloroform, purified by preparative thin layer chromatography and analyzed by gas liquid chromatography/mass spectrometry.

Mono-, di-, tri and tetrachlorobenzenes all yielded only small percentages of phenolic metabolites. Monochlorobenzene and 1,2,3-trichlorobenzene yielded approximately 1% of 4-chlorophenol and 2,3,4-trichlorophenol respectively. 1,3,5-Trichlorobenzene underwent approximately 0.7% conversion to 2,4,6-trichlorophenol; and 1,2,4-trichlorobenzene was metabolized to the same extent to 2,4,5-trichlorophenol. *p*-Dichlorobenzene yielded trace amounts of 2,5-dichlorophenol. Dechlorinated and rearranged metabolites were identified for 1,2,3,5-tetrachlorobenzene (<1.0% 2,3,5-trichlorophenol) and 1,2,4,5-tetrachlorobenzene (<1.0% 2,4,5-trichlorophenol). No metabolites of penta- and hexachlorobenzene were detected for this eight day period.

The formation of 2,3,4,6-tetrachlorophenol from 1,2,3,4-tetrachlorobenzene requires an NIH shift, and suggests that there was an arene oxide intermediate (Daly *et al*., 1972). The metabolites of 1,2,4,5- and 1,2,3,5-tetrachlorobenzene are also typically formed from arene oxide intermediates. As previously mentioned, arene oxide intermediates have been associated with chemical carcinogenicity.

4. Effects on Invertebrates

(a) Insects

Insects can oxidize halogenated benzenes similarly to nonhuman mammalians. Certain oxidations show characteristics which seem to be peculiar to the endoplasmic reticulum (microsomes) of mammalian cells (Hook et al., 1968). The similarities between products of oxidation in both vertebrate and invertebrate systems suggest that enzymes in invertebrate insects may be of the same type as those found in mammals. Most significant is the hydroxylation of the benzene ring with substituents which withdraw or attract electrons. Monochlorobenzene is biotransformed in the locust to o- (1 to 6.9%), m- (2 to 20%), and p-chlorophenols (4 to 33%) and 4-chlorocatechol (10 to 37%) (Hook et al., 1968). The proportion of these isomers varies among the species of insect studied (Hook et al., 1968). Table 85 illustrates the difference in proportion of the chlorophenol isomers among locusts and different mammals.

TABLE 85

SPECTROPHOTOMETRIC ESTIMATION OF CHLOROMONOPHENOLS PRESENT IN HYDROLYSED URINE OF ANIMALS DOSED WITH CHLOROBENZENE

(Gessner and Smith, 1960)

	Expt. no.	% of Dose as Chlorophenols			Ratio (ortho:meta:para)
		ortho	meta	para	
Locusts	1	2.6	2.0	4.2	1.3:1:2.1
	2*	-	4.4	9.4	- :1:2.1
Rabbit	1	1.1	2.8	4.6	0.4:1:1.6
	2	1.2	2.8	6.1	0.4:1:2.2
Rat	1	1.8	2.9	4.9	0.6:1:1.7
	2	2.5	1.8	3.7	1.4:1:2.1
	3	2.8	3.6	6.0	0.8:1:1.7
Ferret	1	1.2	0.8	5.9	1.5:1:7.4
	2	0.4	0.3	2.7	1.3:1:9.0
Cat	1	1.4	3.1	14.9	0.5:1:4.8
	2	1.6	3.1	19.8	0.5:1:6.4

* Estimated by isotopic dilution
Reprinted with permission from Biochem. J., 75(1):175, 1960.

In vitro experiments using homogenates of insects have shown that chlorinated benzenes appear to be oxidized by enzymes similar to mammalian liver endoplasmic enzymes. Homogenates of insects or their organs have yielded products which were inhibitors of oxidations. The inhibitors were sometimes concentrated in a single organ such as the head (Hook et al., 1968). Some inhibitory compounds were removed by centrifugation, but others could not be removed. Satisfactory homogenates for study have been prepared from abdomens and fat bodies. Tissues must also be examined for inhibitors as well as enzymes.

Insects differ widely in their ability to oxidize xenobiotic compounds. House flies are more active than some vertebrate species on a weight basis (Smith, 1967; Hook et al., 1968). In insects, the ability to oxidize the methyl group of p-nitrotoluene decreases in the order: housefly > mustard beetle > German cockroach > cabbage caterpillar > locust > American cockroach > cricket > meal beetle > cotton stainer > grass grub.

The acute effects of insect exposure to chlorinated benzenes are summarized in Table 86. Though both o- and p-dichlorobenzene have been used as insecticides, the latter has found the widest application. However, there are only a limited number of toxicity studies available even for p-dichlorobenzene. Arnold (1957) found that while a low (2.3 to 3.2 mg/l) concentration of p-dichlorobenzene would repel black carpet beetle larvae, higher concentrations were needed to ensure 100% mortality of larvae after four days.

Punt (1950) described initial respiratory and central nervous system stimulation followed by depression in insects exposed to p-dichlorobenzene vapor. After four hours, there was an increase in carbon dioxide output followed by a decrease. The activity of p-dichlorobenzene against insects

TABLE 86

ACUTE EFFECTS OF CHLOROBENZENES IN INSECTS

Chemical	Organism	Exposure	Remarks	Reference
Monochlorobenzene	Locust	*In vitro* homogenates	Gives rise to comparable amounts of *m*- and *p*-phenols	Gessner and Smith, 1960 Hook *et al.*, 1960
o-Dichlorobenzene	*Cimex lectularis*	Fumigant	Nervous system effects (not described)	Cameron *et al.*, 1937
o-Dichlorobenzene	*Dendroctonus pseudotsugae* (Hopk.)	1 part + 5 part diesel oil	100% mortality	Gibson, 1957
p-Dichlorobenzene	*Calandra granaria*	Fumigant	Nervous system effects (not described)	Cameron *et al.*, 1937
	Aphis rumicis	-	Narcosis	Tattersfield *et al.*, 1925.
	Periplaneta americana	Injection	Nervous system effects - increase in activity followed by decrease and spasmodic contractions.	Munson and Yeager, 1945.
	Carabus nemoralis	Vapor	Respiratory and nervous system effects: stimulation followed by depression. Delayed increase in CO_2 output.	Punt, 1950
p-Dichlorobenzene	*Calliphora erthrocephala*	Vapor	-	Punt, 1950
	Tristoma rubrofasciata	Vapor	-	-
	Cambarus virilis	Applied to nerve sheath	Facilitation followed by depression of nerve transmission	-
	Larvae: *Tineola bisselliella* (Hummel) (clothes moth) *Attagenus megatoma* (black carpet beetle)	Vapor at varying temp., 4-9 days	100 % mortality higher temperature kills faster. Shown effective against larvae.	Reith, 1971 -
	Attagenus piceus (Oliv.) (black carpet beetle)	2.3 - 3.2 mg/l	Low concentration repel larvae: very high conc. needed to kill	Arnold, 1957
Trichlorobenzene *p*-Dichlorobenzene	Termites: *Glyptotermes dilatatus* *Kalotermes*	Solid or liquid fumigant	Effective in control. Trichlorobenzene compounds phytotoxic to tea plants	Dantharayana and Fernando, 1970a, 1970b
Trichlorobenzene	*Dendroctonus pseudotsugae* (Douglas Fir beetle)	1 part + 5 parts diesel oil	100% mortality	Gibson, 1957

has been described as similar in nature to DDT, though DDT is the more potent insecticide (Winteringham and Barnes, 1955). Awad (1971) found that a 25% solution of *p*-dichlorobenzene resulted in 100% mortality of the wood borer, *Lyctus africanus*, after eight days. A 5% solution of DDT resulted in 100% mortality in only two days.

Honma (1967) conducted a comparative study of the toxicity of chloro-, bromo- and iodobenzene to *Tyrophagus dimidiatus* (mites). Of the halogenated benzenes tested, monobromobenzene gave the shortest kill time (3 minutes) followed by *o*-dichlorobenzene (4 minutes). *o*-Dibromobenzene was less effective than *o*-dichlorobenzene with a 100% kill time of 20 minutes.

Both monochlorobenzene and monoiodobenzene took 10 minutes to produce 100% mortality. After 20 minutes exposure to 1,2,3-trichlorobenzene, all mites were dead. All halogenated benzenes were dissolved in Tween 20 and water (0.4:9.5); concentration of solutions was 0.5% v/v.

Grosch and Hoffman (1973) investigated the effects of 1,2,3-trichlorobenzene on reproduction of the wasp *Bracon hebetor* Say. A single concentrated dose (0.5 µl) of 10 ppm solution in acetone of 1,3,5-trichlorobenzene was injected between the 2nd and 3rd abdominal segments of *Bracon hebetor* Say virgin females. Each female was placed in its own stender dish with two prestung caterpillars. Eggs were collected daily, immersed in mineral oil, and females and eggs incubated at 30°C. Hatchability was determined at 30 hours. There was a marked increase in mortality of embryos in eggs deposited from the 7th to the 14th day after treatment with 1,2,3-trichlorobenzene. Hatchability prior to the 6th day and after the 15th day did not differ significantly from the controls. The greatest proportion of dead embryos were found among those derived from progenitor cells engaged in mitoses to give oocyte-trophocyte nests (Stage 1 Death). Egg production decreased only slightly.

(b) Marine Organisms and Fresh Water Species

Several chlorinated and fluorinated benzenes are known to be toxic to a variety of marine organisms including molluscs and crustacean species. Because of this known toxicity, there have even been suggestions that mixtures of polychlorinated benzenes be spread around oyster beds to safeguard the crop from predatory species (especially oyster drills). In one test of this possibility, 1,650 lbs. of 40% polychlorobenzene (tri-, tetra-, penta-) were spread over a 1 acre oyster bed in Long Island Sound mixed with low volatile matter (LVM) attapulgus clay to anchor the pesticide to the bottom of the sea bed treated (Ashton and Weil, 1965). Divers inspected the bed six weeks later, and reported that the oyster drills were immobile.

A later study found that a similar mixture called Polystream ® limited the number of drills for at least two years (MacKenzie, 1971). The paper reported that oyster growth was "normal" but made the statement that Polystream ® was toxic to "only small percentages of the fish, clams and crabs". Polystream ® apparently accumulated in oysters and clams after treatment, but the residues "gradually disappeared". No indication was given of the extent of this accumulation, nor the time taken for the residues to disappear.

Davis and Hidu (1969) have reported that a concentration of 3.13 ppm TCB caused an approximately 50% reduction in the number of oyster eggs developing into normal straight-hinge larvae (48 hour TL_m) (see Table 87).

1,3,5-TCB adversely affected the reproductive performance of *Artemia salina* (the brine shrimp). Data are summarized in Table 87 for 1971 studies (Grosch, 1973). In 1972, cultures from the previous year were reconstituted

TABLE 87

EFFECT OF VARIOUS HALOGENATED BENZENES ON INVERTEBRATE MARINE LIFE AND FRESH WATER SPECIES

(a) Marine Organisms

Chemical	Organism	Exposure	Remarks	Reference
o-Dichloro-benzene	hard clams (*Mercenaria mercenaria*)			Davis and Hidu, 1969
	eggs (48 hrs)	100 ppm	TL_m	
	larvae (14 day)	100 ppm		
Trichloro-benzene	American oyster (*Crassostrea virginica*)			
	eggs (48 hrs)	3.13 ppm	TL_m	Davis and Hidu, 1969
	larvae (14 day)	-		
	hard clams			
	eggs (48 hrs)	10 ppm	"	
	larvae (14 day)	10 ppm	"	
Polychloro-benzenes (tri-, tetra- and penta-chlorobenzene, variable isomers and %)	Oyster bed predators esp. oyster drills		Immobilized oyster drills. Tested on 1 acre oyster bed in Long Island Sound - 1,650 lbs of 40% polychlorobenzenes, granular 8-15 mesh using LVM attapulgus clay. Divers inspected over 5-6 weeks, and oyster drills were found immobile.	Ashton and Weil, 1965

TABLE 87 (continued)

Chemical	Organism	Exposure	Remarks	Reference
o-Dichlorobenzene	Oyster drills		Drills would not cross a barrier of ODCB and sand 8" wide [Feb '59 - March '60] extreme swelling in gastropods, immobility and death, curling of tips of rays.	Loosanoff et al., 1960
	Crabs		Lost equilibrium, went into convulsions "ODCB alone does not seriously affect crabs or stop them".	"
Polystream ® (95% active tri-, tetra- and pentachlorobenzene	Oyster drills Eupleura caudata Urosalpinxcinerea cinereus		9.5 kiloliters/hectare killed 85%; low number of drills for at least 2 years; toxic to "only small percentages" of the fish, clams and crabs. After treatment oysters, clams and "other" organisms had small amounts of Polystream ® residues gradually disappeared. Oyster growth normal.	MacKenzie, 1971
o-Dichloro benzene	Oysters (C. virginia)	1 ppm	1 ppm is the minimum concentration which inhibits the growth of young oysters after 24 hours exposure; no accumulation noted, pollutant excreted by organism when chemical removed from the water.	Butler et al., 1960

TABLE 87 (continued)

Chemical	Organism	Exposure	Remarks	Reference
1,3,5-Trichlorobenzene	*Artemia salina* (shrimp)	10 ppm; 24 hrs.	1. Trend toward decrease of life span 2. Delay in appearance of first brood 3. Decrease in average no. of broods per pair 4. Decrease in average no. of zygotes produced	Grosch, 1973
(b) *Fresh Water Species*				
Tetrafluorobenzene	*Biomphalaria glabrata* (host for *Schistosoma mansoni*)	10 ppm	(pH - 5.5) LD_{50}	Duncan and Pavlik, 1970
Hexafluorobenzene	host for *Schistosoma mansoni*	10 ppm	(pH 5.5-7.7, in artificial hard water) LD_{50}	"

by adding distilled water to their contents. All the adults which had survived died in less than a week without producing young.

(5) Effects on Plants

(a) Mutagenicity

p-Dichlorobenzene induces abnormal mitotic division in higher plants. Effects seen include shortening and thickening of chromosomes, precocious separation of chromatids, tetraploid cells, binucleate cells and chromosome bridges (c-mitosis). Available studies are summarized in Table 88.

Abnormal mitotic division of the onion, Allium cepa, on treatment with several halogenated benzenes has been described by Ostergren and Levan (1943). Monochloro-, monobromo and monoiodobenzene at concentrations of 1,000 x 10^{-6} mol caused full c-mitosis disturbances. Partial disturbances (not described) occurred at 300 x 10^{-6} mol. o-Dichlorobenzene produced full c-mitosis abnormalities at 300 x 10^{-6} mol with partial disturbances of mitotic division at 100 x 10^{-6} mol. Trichlorobenzene (1,2,3-) and hexachlorobenzene produced full c-mitosis abnormalities at (100 and 50) x 10^{-6} mols, respectively. Note the decrease in concentrations required to produce full c-mitosis, as number of chlorine atoms increases.

(b) Effect on Germination

p-Dichlorobenzene is added to field crop seeds to control seed storage insects. It was shown that while effective in controlling pests, p-dichlorobenzene significantly decreased the viability of the seeds. This effect was more pronounced when seeds are stored in a closed container rather than an open bin (Day and Thompson, 1965). Oil seed crops, corn, sorghum and wheat were more seriously affected by p-dichlorobenzene than were grasses and legumes.

TABLE 88 EFFECTS OF P-DICHLOROBENZENE ON MITOTIC DIVISION

Organism	Treatment	Frag- ments	Persistence of Fragments	Remarks	Reference
Fenugreek seeds	4-24 hours soak in sat. soln.	-	-	No change in morphology or cytology of seedlings	Gupta, 1972
Fenugreek seedlings	4 hour "exposure"	+	not indicated	Root tip chromosomes contracted and arrested at metaphase	"
	Greater than 4 hours (not specified)	-	-	After "longer" treatment, mitosis appeared normal	"
Six species of monocotyledon angiosperms-root tips	4 1/2 hour soak in sat. soln.	+	+	Frequency of fragments at metaphase tended to decrease. Frequency high-24,48 hrs. and decreased at 72, 96 hrs. 2 plants still highly fragmented at 96 hrs. 1 complete recovery.	Sharma and Bhattacharyya, 1956
Nine species of dicotyledon angiosperms-root tips	1-4 hours depending on plant	+	+	2 plants recovered before 96 hrs. 1 plant died after 48 hrs. 3 plants very highly fragmented at 96 hrs.	"
Three species of *Vicieae* - root tips	4-6 hours in sat. soln.	+	not indicated	c-mitosis abnormalities. Breaks associated with heterochromatic chromosome regions	Srivastava, 1966
Nothoscordum fragrans Kunth					
Root tips	3 1/2 hrs. soak in sat. soln.	+	not indicated	Erosion and fragmentation of chromosomes both at metaphase and anaphase	Sharma and Sarkar, 1957
Root tips	6 hrs. sat. soln.	++	not indicated	Erosion and stickiness, increase in fragments from 3 1/2 hour soak	"
Pollen	6 hours	-	-	No fragmentation, some diplochromosomes. Indication of slight disturbance in spindle mechanism and failure in separation.	"
Fenugreek seeds	4-24 hours soak in sat. soln.	-	-	No changes in morphology or cytology of seeds noted	Gupta, 1972
Fenugreek seedlings	4 hours	+	not indicated	Root tips contracted and arrested at metaphase.	"
"	above 4 hours	-	-	Mitosis appeared normal	"
[Flower buds]	[3 1/2 hrs. sat. soln.]	[-]	[-]	[Meiotic division - only stickiness of chromosomes noted.]	Sharma and Sarkar, 1957
	[6 hrs. sat. sol.]	[-]	[-]	[Lagging, non-disjunction and stickiness of chromosomes. No fragments.]	"

* c-mitosis as in colchicine-mitosis — shortening and thickening of chromosomes, precocious separation of chromatids, tetraploid cells, binucleate cells, chromosome bridges.

+ fragments present

- fragments absent

Seeds were stored in Mesa, Arizona, in open and closed Mason jars (1 qt) containing 25 g of PDCB for up to eight years. No attempt was made to control temperature or humidity. After four years, none of the California Imperial flax seeds (Linum usitatissimum L.) germinated from either the open or the closed test container. The open control registered 77% germination after four years, while the closed control averaged 82%. Arivat barley seeds (Hordeum vulgare. L.) stored in the closed test jar averaged 3% germination after eight years, while germination of the barley seed in the open test jar was 54%. The controls averaged 59% and 72% in the closed and open containers respectively (Day and Thompson, 1965).

After three years, none of the seeds of Pima S-1 fuzzy cotton (Gossypium barbadense L.) from the closed test container germinated (control 58%). After 8 years in the open test container, 43% of the fuzzy cotton seeds germinated (control 68%).

Ameen et al. (1960) studied the effects of 1,2,4,5-tetrachlorobenzene on the germination and seedling vigor of barley, oats and wheat. Four types of soil (sand, loam, clay loam, and clay) were pretreated with tetrachlorobenzene prior to planting of the seeds. Seedling vigor and germination percentage decreased for all four soils. However, damage was most severe in the sandy soil. No germination of barley or oats occurred when planted one day after soil treatment. Planting 25 days after treatment produced 100% germination for barley and 95% for oats. The height of the seedlings increased with time interval between treatment and planting. (This was presumably because tetrachlorobenzene volatilized from the soil.) Barley was more resistant to the tetrachlorobenzene than oats or wheat in the sandy soil. The decrease in seedling vigor and germination percentage was less pronounced for crops grown in clay than in any of the light soils. The one exception was a poor growth performance for seedlings in the clay loam. This was thought to be due to high concentrations of soluble salts (7,700 ppm) present in that soil.

6. Effects on Microorganisms

(a) Fungicidal Effectiveness

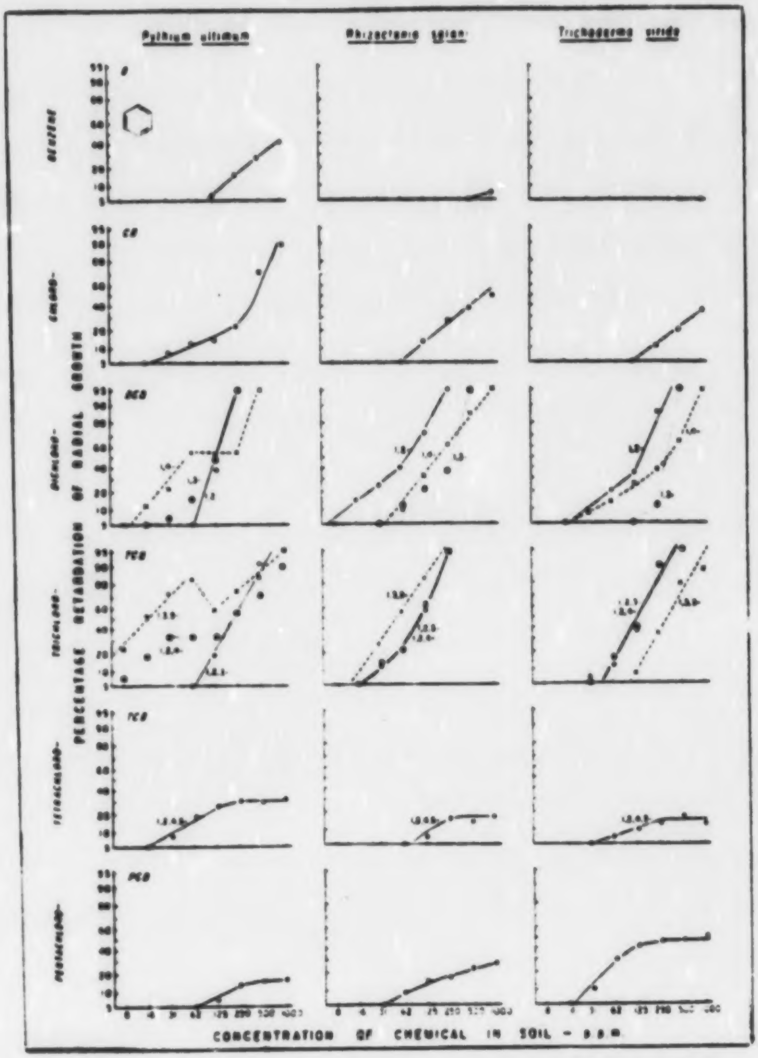
The antifungal vapor phase activity of chlorobenzenes in the soil was investigated by Richardson (1968). A relationship was established between chemical structure and vapor action.

The percentage retardation of radial growth of the three fungal species tested, (*Pythium ultimum*, *Rhizoctonia solani* and *Trichoderma viride*) was greatest for dichloro- and trichlorobenzene. Antifungal activity decreased for tetrachlorobenzene and pentachlorobenzene. Neither benzene nor hexachlorobenzene retarded growth of *T. viride* at 1,000 ppm. While the di- and trichlorinated benzenes were effective against all three fungal species, tetra- and pentachlorobenzene were more species selective. Thus, *P. ultimum* was the most sensitive to 1,2,4,5- tetrachlorobenzene while *T. viride* growth was inhibited to a greater extent by pentachlorobenzene (See Figure 23).

(b) Bactericidal and Sporicidal Efficiency

o-Dichlorobenzene is lethal to *Mycobacterium smegmatis* as both a liquid or a vapor (Crowle, 1958). Torres *et al*. (1970) showed that at a dilution of 1:800, ODCB was active against *Staphylococcus aureus* and *Escherichia coli in vitro*. In the presence of organic matter (10% defibrinated sheep blood), ODCB was effective against the spores of *Bacillus anthracis* after 15 minutes contact. Under the same conditions, excellent bactericidal action was shown against the cells of *Salmonella typhimurium*, *B. anthracis*, *Staphylococcus*

FIGURE 23 DOSE RESPONSES OF FUNGI TO VAPORS OF CHLOROBENZENES IN THE SOIL (Richardson, 1968)



Reprinted with permission of the American Phytopathological Society aureus, and E. coli. According to Brown et al. (1975), p-dichlorobenzene is not toxic to Ustilago maydis.

(c) Effect on Phytoplankton

Ukeles (1962) conducted a laboratory study of the tolerance of five species of marine phytoplankton to concentrations of various toxicants including o-dichlorobenzene. Marine phytoplankton are important food for clams and oysters, and are the base of many marine food chains.

o-Dichlorobenzene had no significant effect on growth of any of the tested species at 8 ppm. At 13 ppm none of the organisms grew, but all were viable. Lethal concentrations were reached at around 80 ppm, and at 130 ppm all species were dead (see Table 89).

Ukeles pointed out that high concentrations of toxicants used for predator control might be "safe" when used in shellfish hatcheries, though hazardous under natural conditions. This is because plankton food is grown apart from the hatchery and periodically added to it. Hence, inhibition of phytoplankton growth would not occur. In nature, phytoplankton blooms are important as a source of food. Therefore, any alteration in growth of phytoplankton resulting from use of halogenated benzenes for predator control could have consequences along the food chain.

(d) Mutagenicity Studies

Anderson et al. (1972) evaluated 110 herbicides for their ability to produce point mutations in a number of different microbial systems (Ames procedures). When tested in a culture of histidine requiring mutants of Salmonella typhimurium, both o-dichlorobenzene and trichlorobenzene (isomer not specified) gave a negative response, i.e., they were not mutagenic. The culture was chosen because of a reported high probability of detecting point

TABLE 89

EFFECTS OF ODCB ON GROWTH OF MARINE PHYTOPLANKTON

Concentration (ppm) of ODCB	Protococcus sp.	Chlorella sp.	Dunarliella euchlora	Phaeodactylum tricornutum	Monochrysis lutheri
1.3	0.71	0.82	0.71	0.74	1.00
7.6	0.80	0.95	0.90	0.80	0.65
13	0.00*	0.00*	0.00*	0.00*	0.00*
130	0.00	0.00	0.00	0.00	0.00
Lindane (ppm) concentration					
7.5	0.75	0.36	0.73	0.00*	0.00
9	1.0	0.33	0.60	0.00*	0.00

* no growth, but organisms viable

All numbers represent the ratio of optical density (o.d.) of growth in the presence of toxicants to o.d. in the basal medium with no added toxicants. Hence 1 = approximately normal growth.

Reprinted with permission from Ukeles, R. Growth of Pure Cultures of Marine Phytoplankton in the Presence of Toxicants. Appl. Microbiol., 10:534, 1962. Copyright © 1962 by American Society for Microbiology.

mutations to single genophores onto the DNA molecule within this system. Pentachlorophenol, a metabolite of pentachlorobenzene, was also negative in this test system. The metabolites of other halogenated benzenes were not evaluated. More specifically, the activated intermediates were not tested as would be the case in a typical Ames assay (Ames *et al*., 1973). Under Ames procedures, a homogenate of the tissues of the species is added to the chemical in order to generate short-lived intermediates.

The spores of the vitamin B_1-deficient mutant *Streptococcus antibioticus 400* were treated with monochlorobenzene (0.05 and 0.1 ml). After 24 hours, all spores were dead. At six hours, the maximum yield of back mutations observed exceeded the controls by a factor of 187 (low dose) and 1400 (high dose). The mutagenic activity was estimated from the frequency of induced reverse mutations from auxotrophic to prototrophic phenotype (Keskinova, 1968).

Prasad (1970) investigated the mutagenic effects of the herbicide 3',4'-dichloropropionanilide and its degradation products including monochlorobenzene and the three dichlorobenzene isomers. The chemicals were evaluated for frequency of back mutation of the methione-requiring ($meth_3$) locus in the fungus, *Aspergillus nidulans*. The mutagenic activity of monochlorobenzene did not differ significantly from the control. The mutagenicity of the dichlorobenzenes increased in the order: *o*-dichlorobenzene - $5/10^6$ spores; *m*-dichlorobenzene - $9/10^6$ spores; *p*-dichlorobenzene - $11/10^6$ spores.

IV. REGULATIONS AND STANDARDS

A. CURRENT REGULATIONS

1. Food, Drug and Cosmetic Act

Monochlorobenzene (MCB) is a solvent in the manufacture of several resins which are used to make articles intended for repeated food contact. It is regulated as a Food Additive under Section 409(c)(1), 72 Stat. 1786; 21 USC 348(c)(1) of the Act. Under special rules published in the Federal Register in 1969, MCB must not exceed a concentration of 500 ppm as a residue in polysulfone resins intended for food-contact use (HEW, 1969). Monochlorobenzene must not exceed 500 ppm as a residue in polycarbonate resins destined for food-contact use (HEW, 1967).

p-Dichlorobenzene reacts in equimolar parts with sodium sulfide to form polyphenylene sulfide resins. Under the same section of the Food and Drug Act, p-dichlorobenzene concentrations must not exceed 0.8 ppm in the finished resin when used to coat articles intended for repeated contact with food (HEW, 1972).

2. Federal Environmental Pesticide Control Act; Food, Drug and Cosmetic Act

All pesticides must be registered with the Environmental Protection Agency under the Federal Environmental Pesticide Control Act of 1972. Forty-three uses of o-dichlorobenzene are registered under Section 3 of this Act. p-Dichlorobenzene has 304 uses while 1,2,4,-trichlorobenzene has five registered with the Office of Pesticide Programs. There are 26 registered under the Act for hexachlorobenzene. Currently one claim is pending for a product containing monochlorobenzene to be used as a disinfectant (EPA, 1977b).

In 1971, monochlorobenzene (MCB) was exempted from the requirement of a tolerance when used as an inert solvent or cosolvent in manufacture of pesticides applied to growing crops before or after emergence from the soil (EPA, 1971). This authority is designated under the Food, Drug and Cosmetic Act, Section 408(d)(2), 68 Stat. 512, 21 USC 346 a(d)(2). MCB must be present in concentrations no greater than 1%. The pesticide should not be used after the edible parts of the plant begin to form. Livestock are not permitted to graze on the treated areas until 48 hours after application.

The chlorinated benzenes registered as pesticides are categorized as Class III toxins i.e., their oral LD_{50}'s range from 500 to 5000 mg/kg and LC_{50}'s are from 0.2 through 20 mg/l (EPA, 1975a). They must, therefore, carry the following precautionary statement on the label:

> Harmful if swallowed (inhaled or absorbed through the skin). Avoid breathing vapors (dust or spray mist). Avoid contact with skin (eyes or clothing). In case of contact immediately flush eyes or skin with plenty of water. Get medical attention if irritation persists.

The human hazard signal word "caution" should be used on the front panel (EPA, 1975a).

3. Air and Water Acts

Chlorobenzene has been designated a hazardous substance under the Federal Water Pollution Control Act Amendments of 1972. Under proposed rules published in the Federal Register on December 30, 1975, monochlorobenzene is a Class B toxin, i.e. LC_{50} value is within the range 1 to 10 ppm for aquatic organisms (EPA, 1975d). Category B substances are so classified because they:

(a) bioaccumulate with a short retention time of the order of 1 week or less; or

(b) are liable to produce tainting of seafood; or

(c) are moderately toxic to aquatic life.

It is proposed that substances in this category should not be discharged into navigable waters, adjoining shorelines or waters of the contiguous zone from vessels or onshore and offshore facilities in quantities exceding 10 pounds (4.54 kg). This value is defined as the harmful quantity (HQ).

In the event of discharges above this value, the authorities must be immediately notified. It is proposed that penalties for exceeding the HQ be based on the behavior of the chemical in water. Monochlorobenzene is defined as an insoluble sinker (i.e. it is heavier than water and insoluble). The proposed penalty for dumping quantities of MCB in excess of the Harmful Quantity is $36 per excess pound dumped. It is also proposed that the dumping of any quantity of designated hazardous substances (including monochlorobenzene) into "special waters" be forbidden. "Special waters" are defined as:

(a) drinking water

(b) waters of the National Wildlife Refuge System

(c) waters of the National Forest Wilderness

(d) waters of the National Park System

(e) waters of the National Wilderness Preservation System

Under 40 CFR 141, Subpart E of the Safe Drinking Water Act, PL. 93-523, a basic monitoring study for organic chemicals in drinking water was established in December 1975. Included in this regulation was a listing of chemicals which "may" be included in the monitoring effort. This list included p-dichlorobenzene and 1,2,4- trichlorobenzene (EPA, 1975c).

4. Other Environmental Protection Agency Authority

In June 1976, EPA issued a Proposed Revision of Regulations and Criteria relating to Ocean Dumping (EPA, 1976b). Under these changes, organohalogen compounds would be prohibited from ocean dumping operations unless present as a trace contaminant. The total concentration of organohalogen constituents within the waste should be less than the toxic concentrations toward marine life, as determined by existing or developed scientific data. This proposed stricture is applicable to all halogenated benzenes.

The EPA Administrator now has authority under Section 608, the Toxic Substances Control Act of 1976, to prohibit manufacture, processing or distribution of hazardous chemicals. He may also limit quantities manufactured for specific uses, require additional labeling and obligate manufacturers both to make and maintain records of processes and to monitor or conduct tests to insure compliance with the Law. This broad authority has not been applied to manufacture and use of halogenated benzenes, though it would be applicable if needed.

The Solid Waste Disposal Act (42 USC 3251) as amended by the Resource Conservation and Recovery ACt of 1976 (PL 94-580) has broad authority over the management of hazardous waste. Criteria for identifying and listing hazardous waste will be developed and published in the Federal Register within 18 months from enactment of the legislation. Once identified, the Act mandates that such waste be accurately labeled, complete records kept of disposal (both quantities and method of disposition), and that all hazardous waste treatment, storage and disposal facilities be run in accordance with Federal regulations. It might be anticipated that certain halogenated benzenes will be included in the list of hazardous wastes.

5. Occupational Safety and Health Administration (OSHA)

Exposure to mono-, o- and p-dichlorobenzene is regulated in the work environment by OSHA under 40 F.R. 23073, May 28, 1975 (OSHA, 1976). A worker may not be exposed to average concentrations of monochlorobenzene exceeding 75 ppm over an eight hour time period. The time weighted average for p-dichlorobenzene is also 75 ppm. o-Dichlorobenzene has a ceiling value of 50 ppm, i.e., worker exposure should at no time exceed this value.

6. Department of Transportation (DOT)

The Department of Transportation (DOT) regulates interstate transport of goods. Overseas transportation is regulated through the Coast Guard. Monochlorobenzene is classified as a flammable liquid (DOT, 1975, 1976). As such, it must be packaged according to DOT specifications. If transported in tank trucks or cars, MCB is exempt from the specification packaging, marking and labeling requirements of the Transport Regulations (173.118) except that the tank cab or trucks must be labeled "flammable liquid". When transported by air in a passenger carrying aircraft, the maximum net quantity permitted is 10 gallons. When carried by water, packages must be identified by labeling according to the contents. In the event of an accident during transportation, the authorities must be immediately notified.

Monobromobenzene is classified as a combustible liquid. No labels are required by DOT regulations. The flashpoint of monobromobenzene is above 73°F. This should be indicated on the outside container. There is no limit to the net quantity contained in one package which may be shipped by air.

Monofluorobenzene, o-, m- and p-difluorobenzene have low flashpoints (9°F, 45°F, 12°F, and 11°F) and require a DOT Red Label.

o-Dichlorobenzene and p-dichlorobenzene are classified as ORM-A hazards. This category is defined as an "Other Regulated Material" which:

> ...has an anesthetic, irritating, noxious, toxic or other similar property and which can cause extreme annoyance or discomfort to passengers and crew in the event of leakage during transportation.

ORM-A liquids with a flashpoint between 100° and 200°F when transported with more than 11 gallons in one container are classified as combustible liquids. Both ODCB and PDCB fall into this category (flashpoints, 160° and 152°F respectively). Hence, when transported in bulk, both dichlorobenzenes must conform to specifications for handling combustible materials.

There is no limit to the quantities of either compound which may be contained in one package transported by air. Additional details of regulated handling procedures for halogenated benzenes in interstate transportation were discussed in Section II D.

The Coast Guard has published warning data sheets for mono, o- and p-dichlorobenzene. All are classified as combustible. In the event of a spill, the local health and pollution control authorities and the local fire department must be notified. Both monochlorobenzene and p-dichlorobenzene are stated to be hazardous to aquatic life in very low concentrations. p-Dichlorobenzene may foul the shoreline. It is also stated that the effects of low concentrations of o- and p-dichlorobenzene on aquatic life are unknown. (U.S. Coast Guard, 1970)

7. State Regulations

A number of states have passed or are considering special legislation regulating the manufacture, use and/or disposal of toxic substances. Very often state legislation mirrors Federal legislation, regulations and guidelines. For example, New Jersey has an Economic Poison Act under which any pesticide used in the State must be registered after submission of a product data sheet to the regulatory department. Only those pesticides registered by EPA under the Federal Environmental Pesticide Control Act are eligible for registration under the State law. Other states have similar regulations governing use of pesticides.

The State of Virginia has implemented a Toxic Substances Information Act (Virginia, 1976) to gather data on hazardous chemicals used in any manufacturing process with the State. As currently amended, use of all substances with a threshold limit value (TLV) should have been reported to the State Board of Health by January 1, 1977. This stipulation applied to mono-, o- and p-dichlorobenzene all of which have TLV's.

Other substances defined as toxic by the enactment must be inventoried by July 1, 1977, when a report documenting the extent and distribution of their usage will be published. A Toxic Substance List has been posted in at least five locations around the state. A toxic substance is defined as any chemical which is:

(a) radiologically active and licensed under the Federal Atomic Energy Act;

(b) listed in the Registry of Toxic Substances;

(c) listed in Water Quality Criteria, Appendices 2 and 3;

(d) registered as a pesticide with EPA.

This regulation is, therefore, applicable to all halogenated benzenes listed in Table 70 (Registry of Toxic Effects).

Currently, the Virginia General Assembly is considering an amendment to modify the Toxic Substances Information Act to apply to any chemical used in a manufacturing process. The House (1454H) and Senate (631S) versions differ slightly, but there is apparently an excellent chance that the listing will become obsolete (Wickline, 1977). On completion of the inventory, the State Health Department will publish a Class I List containing regulations and safeguards controlling usage of the greater risk chemicals. The Department is also interested in determining the prevalence of these chemicals in the watershed and in the environment generally.

Last year, the State of Maryland began a similar inventory of toxic materials "handled" within the State. Materials to be reported were either classified by NIOSH as accepted or suspected carcinogens or were generally toxic materials. No halogenated benzenes were included in this listing. As several firms chose not to reply to the survey, legislation is now pending before the Maryland General Assembly to give the State authority to collect the necessary data.

In 1972, the State of California passed a Hazardous Waste Law to establish regulations and to maintain a program providing for the safe handling and disposal of hazardous wastes. Under regulations effective July 2, 1974, chlorobenzene is defined as a flammable hazardous waste (California Department of Health, 1975). As such, chlorobenzene can only be disposed of at an eligible disposal site by a licensed waste hauler after at least five days notice to the Department of Health. DOT labels are required when hauling MCB to the waste facility. The weight of the waste must be measured or estimated prior to disposal at the site, and submitted to the State along with a State hazardous waste fee. All operators of hazardous waste facilities must submit a monthly report to the State Department of Health.

Colorado regulates controlled disposal of hazardous chemicals in designated landfills. The State has broad authority within these regulations to prohibit certain chemicals from state landfills. This prohibition is decided on a case-by-case basis. It is not known if halogenated benzenes have ever come under this prohibition (Stoddard, 1977).

The State of Oregon has registered *o*-, *p*- and 1,2,4-trichlorobenzene as pesticides for use in the State under ORS Chapter 634 regulated by the State Department of Agriculture. Disposal of pesticides in Oregon is regulated by the Department of Environmental Quality under ORS 459.410-459.690 and OAR Chapter 340, Division 6(3). All pesticides must be disposed of at an Environmentally Hazardous Waste (EHW) facility. While the other halogenated benzenes are not yet formally classified as environmentally hazardous, in practice they are not accepted by other landfills in the State (Oregon, 1977). The State Workmen's Compensation Board regulates handling of chemicals in the work environment as described under OSHA requirements. The Public Utility Commission has adopted Federal DOT rules relating to transport of hazardous chemicals.

Several states are considering new legislation to regulate the manufacture, use, handling, transportation and/or disposal of hazardous wastes. The Texas Water Control Board has jurisdiction over a recently passed State act to control disposal of all types of hazardous waste (including halogenated benzenes). Oklahoma has an Industrial Waste Disposal Act applicable generally to all industrial wastes. Arkansas, Louisiana and New Mexico are all developing inventories of hazardous waste management systems within these states, and are planning to introduce legislation covering disposal of all hazardous wastes (Dyer, 1977).

State water and air pollution authorities follow Federal guidelines in regulating water and air quality standards within each state (see above).

B. CONSENSUS AND SIMILAR STANDARDS

1. Threshold Limit Values (TLVs)

TLV's refer to the time-weighted concentrations for a 7 or 8 hour work day and a 40 hour week. Values above the TLV are permitted, providing that there is an equivalent drop below the TLV that same day. The "C" value assigned to o-dichlorobenzene (ODCB) indicates that this is a ceiling value above which ODCB concentration should not rise (see Table 90).

TABLE 90

ADOPTED THRESHOLD LIMIT VALUES

(American Conference of Governmental Industrial Hygienists, 1971)

Chemical	Concentration	
	ppm	mg/m
Monochlorobenzene	75	350
o-Dichlorobenzene	50	300
p-Dichlorobenzene	75	450

The maximal concentration for MCB exposure is based on analogy with other chemicals, and on limited industrial exposure data (American Industrial Hygiene Association, 1964a). The American Conference of Governmental Industrial Hygienists (ACGIH) has indicated that this value is probably too high, and in fact it is much higher than standards in other countries (see below). The values for ODCB and PDCB are not low enough to prevent eye irritation based on past human sensory response to the vapors (American Industrial Hygiene

Association, 1964a). The American Conference of Governmental Industrial Hygienists recently recommended a time-weighted average of 50 ppm for *p*-dichlorobenzene, based on animal data and human experience and response.

The American Conference of Governmental Industrial Hygienists has published a Notice of Intended Change recommending a 5 ppm ceiling for 1,2,4-trichlorobenzene. In the absence of any established government standard regulating exposure to 1,2,4,5-tetrachlorobenzene, Dow Chemical has suggested a time-weighted average of 0.4 ppm as a conservative guideline for intermediate usage (Dow, 1977a). No TLVs have been established for the other halogenated benzenes. In a list of provisional operational limits published by ACGIH in 1966, the following limits were proposed: 1,2,4-trichlorobenzene, 25 ppm; hexafluorobenzene, 100 ppm; chloropentafluorobenzene, 100 ppm; and 1,3,5-trichlorotrifluorobenzene, 25 ppm.

2. Public Exposure Limits

The American Conference of Governmental Industrial Hygienists recommends the following short-term atmospheric exposure limits based on animal data and human experience (American Industrial Hygiene Association, 1964b):

Monochlorobenzene	2200 ppm for 0.2 hrs daily 4400 ppm for 0.1 hrs daily 8800 ppm for 0.03 hrs daily
o-Dichlorobenzene *p*-Dichlorobenzene*	900-1000 ppm for 2 hrs daily

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*Humans will not voluntarily tolerate acute exposure likely to cause serious health problems.

An atmospheric exposure of 6500 ppm of monochlorobenzene for 1/2 hour or 2000 ppm for one hour should not cause death (American Industrial Hygiene Association, 1964b). A concentration of *o*-dichlorobenzene of 1700 ppm (saturated atmosphere) is not likely to endanger life after a 30 minute exposure. The air concentration of p-dichlorobenzene immediately hazardous to human life is not known, but the saturation concentration at room temperature is not considered imminently dangerous. The 1976 tentative short-term exposure limits (STEL) recommended by the ACGIH are 75 ppm and 50 ppm for monochlorobenzene and o-dichlorobenzene respectively. The tentative STEL for p-dichlorobenzene (PDCB) is 110 ppm (Oak Ridge National Laboratories, 1977).

Little (1968) in a report to the Manufacturing Chemists Association (MCA) listed the odor threshold for MCB as 0.21 ppm for both 50 and 100% response. The odor threshold for ODCB is 2 to 4 ppm (American Industrial Hygiene Association, 1964b). At 10 to 15 ppm, the smell becomes very noticeable, and at around 25 to 30 ppm it is considered unpleasant. Eye irritation becomes a problem at the same concentration range, while at exposures of 60 to 100 ppm, eye and mucous membrane irritation may be very painful. The odor threshold for PDCB is from 15 to 30 ppm for unacclimated persons (American Industrial Hygiene Association, 1964b). Eye irritation begins at around 50 to 80 ppm and exposure becomes painful at 160 ppm.

3. Foreign Standards

As can be seen in Table 91 below, much lower exposure limits are operational in several foreign countries.

TABLE 91

RECOMMENDED MAXIMAL ALLOWABLE CONCENTRATIONS IN OTHER COUNTRIES

Country	Year	Chemical	Concentration	Reference
Soviet Union	1966	Monochlorobenzene	10 ppm	ACGIH, 1971
Czechoslovakia	1969	Monochlorobenzene	43 ppm	ACGIH, 1971
Romania	1960	Monochlorobenzene	0.05 mg/l	Gabor and Raucher, 1960
Soviet Union	1970	o-Dichlorobenzene	20 mg/m^3	International Agency for Research on Cancer, 1974.
Soviet Union	1970	p-Dichlorobenzene	20 mg/m^3	"

4. Other

In 1975, the National Science Foundation sponsored a workshop to identify manufactured organic chemicals of greatest environmental and/or health concern. During Phase I of the study, lists of potentially hazardous materials were drawn up, based on their release rate and known toxicity. Over 337 chemicals were examined individually and rated by panel members on the scale of 0 (no interest) to 5 (highest interest - i.e., as an environmental pollutant). A short list of 80 compounds was selected for further study in Phase II and a final "Hazard Priority Ranking of Manufactured Chemicals" was developed. Hexachlorobenzene, p-dichlorobenzene and o-dichlorobenzene were selected for Phase II study. Table 92 summarizes this ranking and includes other hazardous chemicals to give perspective to the degree of hazard implicit in this listing.

In 1974, Midwest Research Institute produced a report for the Council on Environmental Quality that included a ranking of selected pesticides according to their negative environmental impact. Of 125 pesticides examined, p-dichlorobenzene was ranked 14th in a table of pesticides requiring further study, first in its group of five fumigants and twenty-first in total ranking. For comparison, creosote was ranked first, pentachlorophenol was second, chlordane was third, 2,4-D was twenty-second and aldrin was twenty-fifth (Midwest Research Institute, 1974). These rankings were based on quantities found in the environment and established toxicity data.

TABLE 92

CHEMICALS SELECTED FOR PHASE II STUDY BY THE NSF WORKSHOP PANEL (SHORTENED LIST)

(Brown *et al*., 1975)

Chemical No.	Release Rate Rank	Final Score		Chemical
		Environmental Interest	Health Interest	
4	65	2.60	3.40	Vinyl chloride
5	*	3.90	3.20	Hexachlorobenzene
17	80	4.00	4.25	Carbon tetrachloride
18	131	3.00	2.38	Chlorinated paraffins (35-64% chlorine)
21	56	3.75	4.88	Benzene (chemical uses)
29	100	2.75	2.00	*p*-Dichlorobenzene
31	185	2.63	1.88	*o*-Dichlorobenzene
34	*	4.63	4.13	Polyhalogenated biphenyls
47	60	4.00	4.25	Chloroform
62	237	1.86	1.29	Napthalene

* Not ranked, but nominated as a "Chemical of Particular Concern" by a Panel Member.

SUMMARY AND RECOMMENDATIONS

(a) Summary

Generally, halogenated benzenes are chemically stable. All fluorinated benzenes, monochloro-, o- and m-dichlorobenzene, monobromo-, o- and m-dibromobenzene and monoiodobenzene are colorless liquids at room temperature. Other halogenated benzenes are white crystalline solids. Pentabromobenzene and the tri-, tetra-, penta- and hexasubstituted iodobenzenes have a tendency to sublime. p-Dichlorobenzene (b.p. 174.5°C) also readily sublimes at room temperature.

The halobenzenes are comparatively volatile compounds. They are poorly soluble in water but readily soluble in non-polar solvents and lipids.

Several fluorinated, chlorinated and brominated compounds have low flashpoints. Apart from a tendency of the lower halogenated compounds to react with oxidizing agents, the chemical stability of the group is good. Halogenated benzenes are neutral compounds that are generally unreactive to acids, alkalis and other common laboratory reagents. Lower substituted halogenated compounds are especially resistant to nucleophilic attack, but substitution by additional halides increases susceptibility to nucleophiles. The reverse is true for electrophilic substitution, where lower halogenated compounds are more easily attacked by electrophiles. Several halobenzenes form organometallic compounds of great use in organic synthesis.

Of the halogenated benzenes studied, only the chlorinated compounds are produced in bulk. There has been a recent tendency to introduce mixed halogen compounds (e.g. p-bromochlorobenzene and o-chlorofluorobenzene) that have properties similar to the chlorinated compounds in order to obtain products with more desirable characteristics.

Presently, over 300 million pounds of monochlorobenzene are produced annually in this country alone; however, this figure is down almost 50% from the 1969 high. Production of o-dichlorobenzene was nearly 55 million pounds in 1975, while p-dichlorobenzene production in 1975 was about 46 million pounds. Production of o- and p-dichlorobenzene has also dropped off somewhat from previous years. 1,2,4-Trichlorobenzene is also a major industrial chemical; in 1973, just over 28 million pounds were produced. Production of 1,2,4,5-tetrachlorobenzene was estimated at 18 million pounds for 1973. Substantial amounts (about two million pounds each) of monochlorobenzene, o-dichlorobenzene, 1,2,4-trichlorobenzene and 1,2,4,5-tetrachlorobenzene, as well as lesser amounts of other chlorinated benzenes, were reportedly imported during 1971 to 1975.

Monobromobenzene and bromochlorobenzene appear to be the most commercially important of the brominated compounds. Fluorinated benzenes are expensive, and a market for higher fluorinated derivatives has not developed. Monoiodobenzene and diiodobenzenes have limited industrial application.

Chlorinated benzenes are basically used for five purposes: (i) as solvents; (ii) as functional fluids (heat transfer and in dielectric mixtures); (iii) as chemical intermediates, especially for the manufacture of phenolic compounds, herbicides and dyes; (iv) as insect repellents or pesticides, (v) for deodorizing. Other halogenated benzenes are either chemical intermediates or solvents.

Environmental contamination occurs during manufacture of chlorobenzenes. During production, an estimated 0.00488 kg of monochlorobenzene enters the waste stream for every kilogram of monochlorobenzene produced. Estimated losses of dichlorobenzenes during manufacture are 0.0038 kg/kg monochlorobenzene produced. A "polychlorinated sludge" is also produced. Annual loss to the environment during manufacture of o-dichlorobenzene has been estimated at 0.9 million pounds/year, and for p-dichlorobenzene at 1.2 million pounds per annum.

Apart from losses during manufacture, there is also environmental contamination resulting from use of chlorinated benzenes. Monochlorobenzene and o-dichlorobenzene enter the environment when used as solvents, especially for toluene diisocyanate production. Lower chlorinated benzenes also enter the environment when used as dye-carrier solvents. o-Dichlorobenzene is apparently being deliberately added to treated industrial wastewater to mask odor. It has been estimated that nearly 70 million pounds of p-dichlorobenzene are used annually for moth control or as a space odorant. Presumably each year a similar quantity sublimes into the atmosphere. Chlorinated benzenes may also be entering the environment as break-down products of the pesticides, lindane, pentachloronitrobenzene and hexachlorobenzene, or may be present in these chemicals as impurities.

Chlorinated benzenes have been found in drinking water and raw water sources in the United States and in Europe. Trichlorobenzene has been detected in fish caught in Lake Superior and Lake Huron. There are several European reports of pentachlorobenzene accumulation in soil and in vegetables treated with hexachlorobenzene. p-Dichlorobenzene has been detected in human blood samples in this country, and with 1,2,4,5-tetrachlorobenzene and hexachlorobenzene, has been identified in human blood and adipose tissue in Japan.

As previously mentioned, chemical characteristics of the halogenated benzenes vary with degree of substitution and type of halogen substituted. Biological properties are remarkably similar for all halogenated benzenes in a given series, e.g. all the monosubstituted compounds or all disubstituted halobenzenes. Slight differences in biological effects appear to be related to isosteric characteristics.

In general, halogenated benzenes appear to produce central nervous system effects. These effects may be either stimulation or depression. Most of the acute effects are reversible if the chemicals are withdrawn. Depression of the CNS may proceed to anesthesia. Accompanying the depression may be some analgesic effects. The fluorinated compounds appear to have the best analgesic properties, and the least potential for producing toxicity. There is a species difference in the ability of halogenated benzenes to produce CNS effects, for example, in dogs the polyfluorinated benzenes appear to be quite analgesic, whereas in mice they are not.

Several studies described alterations in conditioned reflexes of rats fed monochlorobenzene, o-dichlorobenzene or tetrachlorobenzene. As the halogenated benzenes produce central nervous system effects, it is reasonable to expect that there may be other behavioral effects not yet described.

There is at least one study suggesting that perhaps p-dichlorobenzene modified the induced resistance of rats to leukemia. Monochlorobenzene has been shown to interfere with the Schwartzman phenomenon. No other evidence was found that halogenated benzenes are immunosuppressants, though as halogenated benzenes affect the central nervous system which has some control over immune responses, this remains an unexplored possibility.

In terms of acute toxicity, the halogenated benzenes are not highly toxic compounds. But in all the subacute or chronic toxicity studies, biological effects are evident at comparatively low concentrations. For the halogenated benzenes there is no relationship between acute toxicity and the ability of the compound to produce damage.

In general, halobenzenes are metabolized by hydroxylation with possible formation of an arene oxide intermediate. The arene oxide intermediate appears to be responsible for chronic effects, such as necrosis in liver, lung and kidney. The effects of the arene oxide metabolite can, however, be mitigated by other metabolic and, perhaps, genetic factors. Only those halogenated benzenes with a free vicinal position are capable of forming such toxic intermediates, but do not necessarily do so. Resistance to the formation of the arene oxide intermediate by fluorinated benzenes and the p-disubstituted halogenated benzenes is well documented.

All halogenated benzenes appear to be highly lipid soluble. Although there are very few data on partition coefficients, for the chlorinated series there appears to be an increase in value of partition coefficient as degree of chlorination increases. A high value of partition coeffecient is associated with accumulation in the lipids of organisms. Also, as the number of halogens increases, the compounds are apparently more resistant to biodegradation. These factors suggest that the higher-substituted chlorinated benzenes are more likely to bioaccumulate than the lower-substituted compounds. However, also a factor in bioaccumulation is the rate of absorption into the system, which appears to decrease as chlorination increases. Thus, it becomes obvious that opposite forces are at work, perhaps in favor of the accumulation of the lower or the higher chlorinated benzenes.

If all forces are taken into consideration and remembering that significant amounts of the monohalogenated benzenes are excreted unchanged in expired air, it would appear that all chlorinated benzenes tend to accumulate in the environment. Alternatively, the quantities of chlorinated and brominated benzenes detected in the environment may reflect an increased monitoring effort or an improvement in methods of detection.

Every halogenated benzene investigated appears to induce porphyria though not to the same degree. This ability to induce porphyria may be closely related to an induction effect on cytochrome P- drug metabolizing enzymes located in the endoplasmic reticulum. In the late 1950's, there was an outbreak of several cases of porphyria in man after ingestion of wheat contaminated by hexachlorobenzene. Symptoms subsided when the wheat was replaced by uncontaminated grain.

Since it is generally known from laboratory experiments that certain pesticides likewise induce porphyria and that these pesticides are also environmental contaminants, it seems highly possible that these substances may be either additive or synergistic in terms of their porphyria-producing characteristics. The combined effects of chemicals as they might occur in the environment have not been studied.

Halogenated benzenes are metabolized by those enzymes associated with the biosynthesis of cholesterol, the catabolism of bile acids and the oxidation of prostaglandins. However, no studies were found which described the effects of halogenated benzenes on the metabolism of endogenous substances.

The mutagenicity and carcinogenicity of the halogenated benzenes have not been well documented in mammals. In some plants exposed to p-dichlorobenzene there appears to be reasonable evidence for mutagenic effects. Inhibition of mitosis has also been reported, though in one study the germination of spores was unaffected. In the only study of its kind identified, o-dichlorobenzene and trichlorobenzene did not produce point mutations in microorganisms. One of the metabolites of pentachlorobenzene, pentachlorophenol, was also negative in this test system. The metabolites of other halogenated benzenes were not evaluated. More specifically, the activated intermediates have not been tested, as would be the case in a typical Ames assay.

There were scattered reports of carcinogenicity in man and animals. The chronic toxicity studies of Hollingsworth are inconclusive as to the carcinogenicity of o- and p-dichlorobenzene. While there was no evidence of hyperplasia, these studies were of too short a duration to rule out definitely the possibility of carcinogenic activity in these two compounds. Other chronic studies (seven to eight months) with tri- and tetrachlorobenzenes in rats gave no evidence of hyperplasia, though one 82-day study of monochlorobenzene in rats did show hyperplasia.

In man, there are several reports of blood dyscrasias apparently caused by chlorinated benzenes. To a certain extent these results are confirmed in experimental animals. In general, other effects which appear to be confirmed in laboratory animals are the eye and skin effects which reportedly have appeared in man on exposure to several of the chlorinated benzenes.

For the most part, halobenzenes have not been tested for reproductive effects or teratogenicity in mammals; therefore, it is not possible to make generalized conclusions regarding effects on reproduction. There were two carefully controlled studies investigating the reproductive effects of 1,3,5-trichlorobenzene on (i) the brine shrimp and (ii) a species of wasp. For both arthropods, results were positive for a slight decrease in life span of adult, delayed appearance of first brood, decrease in average number of offspring, and also a decrease in number of zygotes produced. In addition, in the study on the wasp, evidence was presented that 1,2,3-trichlorobenzene interferes with the mitotic apparatus of the ovariole sequence.

Teratogenic studies are also lacking for any species. The few studies which have evaluated the effects of penta- and hexachlorobenzene in the pregnant rat have shown teratogenic effects for these two compounds.

(b) Recommendations

1. There is a need for long-term, low-dose studies to establish the carcinogenic risk of exposure to chlorinated benzenes. The higher chlorinated benzenes must be studied because of their persistence. Pentachlorobenzene in particular resists biodegradation and is apparently accumulating in the environment with hexachlorobenzene. Human exposure to the lower chlorinated benzenes is great, and hence, although it appears that the anticipated tests may be negative, there is also a high priority for testing these compounds by current carcinogenic methodologies.
2. There is very little information on behavioral effects as a result of exposure to chlorinated benzenes. All of those compounds which have been detected in the environment should be studied for behavioral effects in animals.
3. Possible synergistic effects with other environmental contaminants need further study since the halogenated benzenes interact with cytochrome P-450 as do many other environmental contaminants and endogenous steroids.
4. As compounds which interact with cytochrome P-450 and other drug metabolizing enzymes, there is also a need to evaluate the effects of chlorinated benzenes on the metabolism of endogenous substances including all steroids (adrenal, cortical, reproductive and progesterones) and Vitamin D. The ability of the halobenzenes to induce hypovitaminosis (D) should also be investigated.
5. There should be studies designed to evaluate the effects of chlorinated benzenes on reproductive capacity. The compounds which should be evalu-

ated are those found in the environment to the greatest extent, namely, mono-, o-di-, p-di, 1,2,4-tri-, 1,2,4,5-tetra-, penta-, and hexachlorobenzene as well as monobromobenzene and p-bromochlorobenzene.

6. The scattered reports of immunosuppression found in the literature do not in themselves justify the testing of halogenated benzenes for immunosuppression. However, since the halogenated benzenes appear to affect the nervous system, which in turn is known to have some control over immune responses, it is felt that immunosuppressive effects should be examined for the halogenated benzenes.

7. There is a definite need to establish the behavior of chlorinated benzenes in the environment. For the lower chlorinated compounds especially, there are few data describing environmental fate and transportation. While the lower compounds appear to be biodegradable, the products of degradation must be identified. The rate of disappearance of chlorinated benzenes from the environment also needs to be investigated. More studies are required to establish the extent of transport from water to air, and aerial fallout.

8. The extent of any possible bioaccumulation of chlorinated benzenes should be quantified and should include monitoring of aquatic species (microorganisms, animals and plants).

9. It would also be valuable to establish the extent of environmental contamination resulting from home use of p-dichlorobenzene including use in toilet-blocks. Similarly, the extent of use of o-dichlorobenzene as a sewage deodorant requires immediate documentation.

It should be pointed out that environmental contamination by chlorinated benzenes especially is widespread and likely to continue. No constraint has been placed upon production and use of chlorinated benzenes to date. It is clear that there is insufficient ecotoxicological evidence to assess the degree of hazard presented to human health and the environment by exposure to chlorinated benzenes. However, there is sufficient information available to suggest that chlorinated benzenes may pose some risk. The extent of this risk should be determined.

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